Supreme Court, U.S.
FILED

No. 02-1061

DEC 9 2003
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In The

Supreme Court of the United States

aaiPHARMA INC.,

Petitioner,

v.

TOMMY G. THOMPSON,
Secretary of Health and Human Services;
MARK B. McCLELLAN, M.D., Commissioner of the United States Food and Drug Administration;
UNITED STATES FOOD AND DRUG ADMINISTRATION,

Respondents,

BARR LABORATORIES, INC.;
PAR PHARMACEUTICAL, INC.,

Intervenors.

ON PETITION FOR WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

PETITION FOR WRIT OF CERTIORARI

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QUESTIONS PRESENTED

1. Did the court of appeals err by finding a federal agency's regulation to be a permissible construction of a statute under step two of Chevron U.S.A., Inc. v. Natural Res. Def Council, Inc., 467 U.S. 837 (1984), where that regulation deprived the petitioner of any remedy for the acknowledged violation of its rights under the statute, and where the regulation granted a self-interested private party unreviewable discretion to prevent the petitioner from exercising its statutory rights?

2. Did the court of appeals err under step one of Chevron by finding a statutory provision imposing an enforcement duty on a federal agency to be ambiguous, even though the meaning of the provision was plain, by finding a "conflict" between that provision and a second provision that addressed the agency's role under a different set of circumstances?

CORPORATE CERTIFICATION

aaiPharma has no parent corporation, and no publicly held company owns more than ten percent of its stock. See S.Ct. Rule 29.

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aaiPharma Inc. ("aaiPharma") respectfully petitions for a writ of certiorari to review the judgment of the United States Court of Appeals for the Fourth Circuit in this case.

OPINIONS BELOW

The opinion of the court of appeals (App., infra, at 2-28) is reported at 296 F.3d 227. The opinion of the district court (App., infra, at 29-46) is not reported.

JURISDICTION

The court of appeals entered its judgment on August 26, 2002. aaiPharma's Petition for Rehearing with Petition for Rehearing En Banc was denied on September 9, 2002. App., infra, at 49-50. The jurisdiction of this Court is invoked pursuant to 28 U.S.C.§ 1254(1).

STATUTORY PROVISIONS INVOLVED

5 U.S.C. § 706(A)(2) provides in pertinent part that courts "shall ... hold unlawful and set aside agency actions ... found to be ... arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law."

21 U.S.C. § 355(b)(1) provides in pertinent part:

> The applicant [for a New Drug Application] shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.

21 U.S.C. § 355(c)(2) provides in pertinent part:

> If the patent information described in subsection (b) could not be filed with the submission of an application under subsection (b) of this section because the application was filed before the patent information was required under subsection (b) of this section or a patent was issued after the application was approved under such subsection, the holder of an approved application shall file with the Secretary, the patent number and expiration date of any patent which claims the drug for which the application was submitted or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.

21 U.S.C. § 355(d)(6) provides in pertinent part that if after notice and an opportunity for a hearing "the Secretary finds . . . the [New Drug] application failed to contain the patent information prescribed by subsection (b) . . . he shall issue an order refusing to approve the application . . . "

21 U.S.C. § 355(e)(4) provides in pertinent part that "the Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an [New Drug] application with respect to any drug under this section if the Secretary finds . . . (4) the patent information prescribed by subsection (c) of this section was not filed within thirty days after the receipt of written notice from the Secretary specifying the failure to file such information . . ."[1]

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[1]These statutory provisions, together with the FDA regulation at issue, are reproduced in the Appendix.

STATEMENT

This case presents the question whether a federal agency's interpretation of its governing statute that leaves a party with no remedy for a violation of its statutory rights can be "permissible," and entitled to "deference," under Chevron U.S.A., Inc. v. Natural Res. Def. Council, Inc., 467 U.S. 837, 843-44 (1984). In construing a regulation of the U.S. Food and Drug Administration ("FDA") under the Hatch-Waxman Amendments to the Federal Food, Drug and Cosmetic Act (the "FDA Act"), the Fourth Circuit announced the principle that an agency may relegate itself to a "purely ministerial" role in administering a statute, even when the result is that a self-interested private party can, with impunity, "abuse" the FDA regulatory process set forth in the statute to deprive a patentee of its "clear" statutory right to obtain a thirty-month stay barring the approval of generic drugs infringing its patent. App., infra, at 14. The Fourth Circuit's approval of the FDA regulation at issue, although couched in terms of straightforward Chevron analysis, conflicts with two principles of such fundamental importance (as well as the precedents of this Court and the courts of appeal) that review is warranted: (1) that there must be a remedy for every violation of a statutory right; and (2) that a party's statutory rights cannot be made subject to the unreviewable discretion of a self-interested private party.

This case also presents an important issue of statutory construction, namely whether under Chevron a court can create ambiguity, despite the plain meaning of a statutory provision, by incorrectly determining that the provision is "inconsistent" with another provision of the same statute. The Fourth Circuit acknowledged that the plain language of the Hatch-Waxman Act required the FDA actively to enforce the statute in the situation presented by this case. Instead of ending the inquiry there, the Fourth Circuit improperly found ambiguity based on a

misperceived conflict between the provision at issue and another provision, applying to a different set of circumstances, that the court read as specifying a passive, or "ministerial," role for the FDA. This Court should accept review to confirm that where the meaning of a statute is plain, the inquiry ends there and Chevron step-two analysis is not appropriate.

1. Statutory and Factual Background

a. *The Hatch-Waxman Act's Patent Listing Requirements.* Under the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 321 et. seq. (the "FDA Act"), all prescription drugs must receive FDA approval before they can be marketed. A drug manufacturer wishing to market a new drug containing an active ingredient not previously approved must complete and submit to the FDA a New Drug Application ("NDA") to obtain approval. 21 U.S.C. § 355(a). In 1984, the FDA Act was modified by the Drug Price Competition and Patent Term Restoration Act of 1984, Pub.L. No. 98-417, 98 Stat. 1585 (1984), codified at 21 U.S.C. §§ 355, 360cc, and 35 U.S.C. §§ 156, 271, 282 (the "Hatch-Waxman Act"). See Eli Lilly and Co. v. Medtronic, Inc., 469 U.S. 661 (1990). The Hatch-Waxman Act enacted authority and streamlined procedures for bringing generic drugs to market while at the same time giving additional protection to the owners of patents whose rights might be infringed by the manufacture and distribution of generic drugs. See, e.g., Mylan Pharm., Inc. v. Thompson, 268 F.3d 1323, 1326 (D.C. Cir. 2001).

The Hatch-Waxman Act requires that the NDA applicant submit information to the FDA identifying the number and expiration date of "any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in

the manufacture, use, or sale of the drug." 21 U.S.C. § 355(b)(1). Applicants must also amend NDAs to include such information about any patents required to be listed that issue while the NDA is under review. Id. In addition, and most pertinent to this case, if a patent required to be listed issues after approval of an NDA, the holder of the approved NDA *must* inform the FDA within thirty days after issuance of the patent of the same information required in new or pending NDAs. 21 U.S.C. § 355(c)(2).

b. *The FDA's Obligations Under the Hatch-Waxman Act.* The FDA is required to publish, in a publication known as the "Orange Book," and entitled "Approved Drug Products with Therapeutic Equivalence Evaluations," information on all eligible patents: (1) identified by an NDA applicant during the pendency of an NDA, 21 U.S.C. § 355(b)(1); or (2) or submitted to the FDA by the application holder after approval of an NDA. 21 U.S.C. §§ 355(c)(2), 355(j)(7)(A)(iii). In addition, the statute imposes on the FDA certain enforcement obligations to ensure that NDA applicants and holders comply with the patent listing requirements. Specifically, the FDA is *required* by the statute, after notice and opportunity for hearing, to deny approval of an NDA when the applicant fails to comply with its obligations under subsection (b)(1) to submit patent information for eligible patents, 21 U.S.C. § 355(d)(6), and to withdraw approval of an NDA when the NDA holder fails to comply with its obligations under subsection (c)(2) to submit patent information for eligible patents issued subsequent to approval. 21 U.S.C. § 355(e)(4). Congress' unambiguous use of the word "shall" leaves no room for doubt that these enforcement obligations are mandatory. 21 U.S.C. § 355(d)(6) (". . . [the Secretary] shall issue an order refusing to approve the application"); 21

U.S.C. § 355 (e)(4) ("The Secretary shall . . . withdraw approval of an application . . .").[2]

c. *The Generic Drug Approval Process and the Protections Afforded to Patent Owners by the Listing Requirements.* The patent listing requirements of the Hatch-Waxman Act, and the FDA's statutory obligation to enforce them, are critical because of the rights they afford to owners of eligible patents in relation to manufacturers of generic drugs, most importantly the right to obtain a thirty-month stay of approval of generic drugs to litigate infringement issues prior to marketing. Under the Hatch-Waxman Act, instead of preparing an NDA, the sponsor of a generic drug can submit an Abbreviated New Drug Application ("ANDA"). 21 U.S.C. § 355(j). Unlike an NDA holder who bears the burden of proving to FDA that a new drug product is safe and effective, the generic manufacturer bears only the considerably lesser burden of showing that its product has the same active ingredient, labeling content, dosage form, bioequivalence, and other characteristics as the approved drug. 21 U.S.C. § 355(j)(2).

Prior to the Hatch-Waxman Act, the premarketing use of a patented drug for testing and investigation to meet FDA approval requirements was an act of infringement, Roche Prod. Inc. v. Bolar Pharm. Co., 733 F.2d 858 (Fed. Cir. 1984), thus all but ensuring resolution of infringement issues prior to marketing. The Hatch-Waxman Act, however, stripped patent owners of the right to sue for such activities, instead providing that "it is not infringement to conduct otherwise infringing acts [such as development] necessary to prepare an ANDA." Mylan Pharm., 268 F.3d at 1326; 35 U.S.C. § 271(e)(1). Pursuant to the Hatch-Waxman Act,

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[2]The statute commands the FDA to withdraw NDA approval after giving notice to the NDA holder and providing an opportunity for hearing whether a patent is in fact eligible for listing. In the posture of the proceedings below, the eligibility of aaiPharma's patent was necessarily assumed. App., infra, at 14, n 5.

infringement occurs only when the generic manufacturer files an ANDA to obtain FDA approval for the purpose of marketing a generic drug product claimed in a patent before the patent expires. 35 U.S.C. § 271(e)(2). In exchange for pushing back the timetable for a patent owner to bring an infringement suit, the Hatch-Waxman Act provided for a thirty-month stay of approval upon the filing of suit, thus continuing to ensure resolution of patent infringement issues prior to marketing of generic drugs.

Under the statute, to protect the rights of patent owners, the ANDA applicant must certify to FDA that the generic version will not infringe any patents listed in the Orange Book. Specifically, the generic manufacturer must certify to one of the following "with respect to each patent" that claims the drug or the same use for the drug for which the generic seeks approval: (I) that patent information has not been submitted to the FDA; (II) that the patent has expired; (III) that the patent will expire on a certain date (prior to marketing by the generic); or (IV) that the patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted. 21 U.S.C. § 355(j)(2)(vii)(I-IV).

When an ANDA applicant submits a "Paragraph IV" certification, the applicant must notify the patent owner (and the NDA holder) and provide a detailed statement of the basis for the ANDA applicant's opinion that the patent is invalid and/or will not be infringed. 21 U.S.C. § 355(j)(2)(B)(i)-(ii). The statute then provides that the patent owner has 45 days to initiate a lawsuit against the ANDA applicant for patent infringement. Filing of a suit by the patent owner delays the approval of the ANDA for a thirty-month period, unless a court's decision or order results in a different period. Id. Orange Book listing is thus crucial: "If a patent is not listed in the Orange Book, ANDA applicants do not have to file a paragraph IV certification, and the patent holder is unable to take advantage of the thirty-month stay." App., infra, at 8.

d. *The FDA's Abdication of its Statutory Enforcement Role.* Notwithstanding the mandatory provisions of 21 U.S.C. § 355(d)(6) and (e)(4), the FDA has abdicated its enforcement role by declaring not only that it will simply accept for Orange Book listing those patents that an NDA holder chooses to identify, but also that it will not examine whether patents the NDA holder has not identified are in fact appropriate for listing, even when called to the agency's attention by the *patent owner.* The most consequential expression of the FDA's abdication appears at 21 C.F.R. § 314.53(f):

> If any person disputes the accuracy or relevance of patent information submitted to the agency under this section and published by FDA in the list, or believes that an applicant has failed to submit required patent information, that person must first notify the agency in writing stating the grounds for disagreement . . . . The agency will then request of the applicable [NDA] holder that the correctness of the patent information or omission of patent information be confirmed. Unless the application holder withdraws or amends its patent information in response to FDA's request, the agency will not change the patent information in the list . . . .

(emphasis supplied). The FDA confirms in the preamble to its regulation that it will not fulfill its statutory duties: "[T]he agency declines . . . to ensure that patent information is complete and relevant to an NDA and to confirm, upon request, the validity of patent information submitted to the agency." 59 Fed.Reg. at 50,345. The FDA justifies its refusal to engage in listing disputes by claiming the agency has neither the expertise nor the resources to evaluate patents substantively, despite the statutory mandate. Id.

e. *aaiPharma's '853 Patent, Lilly's Refusal to Identify it in the Prozac® NDA, and the FDA's Failure to Enforce the Hatch-Waxman Act Against Lilly.* On July 10, 2001, the United States Patent and Trademark Office issued U.S. Patent No. 6,258,853 (the "'853 Patent") to aaiPharma, a small pharmaceutical company extensively involved in drug research and development. App., infra, at 8. The '853 Patent describes and claims pharmaceutical formulations comprising the Form A component of fluoxetine hydrochloride at specified purity levels, and methods of using these formulations. Id. at 32. Fluoxetine hydrochloride, a member of the class of antidepressants known as Selective Serotonin Reuptake Inhibitors ("SSRIs"), is the active pharmaceutical ingredient in Eli Lilly & Co.'s ("Lilly") Prozac® drug product. Form A of fluoxetine hydrochloride is a polymorphic variant, or component, of fluoxetine hydrochloride. Id. at 34. The '853 patent meets the statutory criteria under 21 U.S.C. § 355(c)(2) for being identified to the FDA by Lilly because it claims a polymorphic component of fluoxetine hydrochloride, the active ingredient of the drug for which Lilly received NDA approval, and because a claim of patent infringement could reasonably be asserted (and, in fact, has been asserted) against generic drug manufacturers not licensed by aaiPharma to engage in the manufacture, use, or sale of an FDA-approved generic fluoxetine drug which satisfied the claims of the '853 patent. App., infra, at 32, 39.

After the '853 patent issued, aaiPharma asked Lilly to submit patent information to the FDA identifying the '853 patent. However, Lilly refused to do so. App., infra, at 34. On July 18, 2001, aaiPharma sent a letter to the FDA requesting that it vindicate its patent rights under the Hatch-Waxman Act. Id. Although the statute required Lilly to amend its patent information for Prozac® to include eligible patents like the '853 patent for listing in the Orange Book, and although 21 U.S.C. § 355(e)(4) clearly required the FDA to enforce this obligation, the FDA declined to take any

action against Lilly or to take any other action to determine the Orange Book listing eligibility of the identified aaiPharma patent. Consistent with 21 C.F.R. § 314.53(f), the FDA's only response was to send a letter advising Lilly of aaiPharma's concerns but confirming that the agency would not list aaiPharma's patent unless Lilly first identified the patent. App., infra, at 34, 99-100. The FDA's letter threatened no recourse if Lilly did not identify the '853 patent. Id. at 10, 34.

Lilly's claim for exclusivity under the patent laws for Prozac® expired on or about August 2, 2001. App., infra, at 35. Prior to that date a number of companies submitted ANDAs for generic versions of Prozac®, some of which had received final approval effective August 2, 2001, and others of which had received interim approval as of that date. Id. However, because patent information for the '853 patent was not submitted to FDA by Lilly or published by FDA in the Orange Book, those companies were able to avoid submitting Paragraph IV certifications to aaiPharma as the patent owner claiming invalidity or non-infringement of the '853 patent. In turn, aaiPharma was deprived of its right to obtain a thirty-month stay of approvals to litigate infringement issues before marketing. Id.

2. Proceedings Below

On August 2, 2001, aaiPharma filed suit, alleging that the FDA had violated the Administrative Procedures Act by failing to exercise its authority under the Hatch-Waxman Act to require Lilly to identify the '853 patent for publication in the Orange Book. On the same day, after a non-evidentiary hearing, the district court denied from the bench aaiPharma's motion for a temporary restraining order that would have enjoined the FDA from approving generic versions of Prozac® until the eligibility of the '853 patent had been determined. On August 13, 2001, the district court issued an opinion and order confirming the denial of the

motion in which it also held sua sponte that "because the order effectively is a ruling against aai on the merits, the Clerk of Court is directed to enter judgment and to close the file." App., infra, at 46.

The court of appeals affirmed. It held that the district court erred in entering judgment sua sponte where the only proceeding in the case had been the non-evidentiary hearing on aaiPharma's motion for a temporary restraining order, but that "special circumstances" allowed it to "put aside" that error and render a decision on the merits. App., infra, at 12. On the merits, the court of appeals agreed with aaiPharma that if "the '853 patent claims Prozac® . . . , Lilly is obligated to submit the '853 patent for listing in the Orange Book and the FDA is required to publish the submitted listing." Id. at 14. Nonetheless, the court concluded that aaiPharma lacked any remedy for its "legitimate grievance" that it had been deprived of an important statutory right, because there was an "enforcement gap" in the statute that the FDA was not obligated to fill. Id. at 15, 27-28.[3]

The court of appeals reached this result through an improper analysis of the Hatch-Waxman Act that violated both steps of Chevron. First, although acknowledging that subsection (e)(4), "considered in isolation," "could arguably qualify as [a] clear expression[ ] of congressional intent about the proper role of the FDA in Orange Book listing disputes," the court -- instead of holding that plain language dispositive under step one of Chevron -- found that the statute was ambiguous. App., infra, at 19. It did so based on a contrived conflict between the FDA's mandatory enforcement role under subsection (e)(4) when an NDA holder *fails* to identify an eligible patent, and what it found to be the FDA's "purely ministerial role" under subsection (c)(2), which provides that the FDA "shall" list patents that *are* identified by the NDA holder. App., infra, at 19-20.

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[3]Because there is no private right of action under the FDA Act, aaiPharma could not have sued Lilly. App., infra, at 15-16.

Second, the court of appeals concluded that the FDA's regulation limiting itself to a ministerial role in cases of failure to identify eligible patents was "reasonable," and was entitled to deference under step two of Chevron, by misinterpreting subsections (d)(6) and (e)(4) in a manner that had no support in their language or legislative history, and was not even advanced by the agency itself. The court first eviscerated subsection (d)(6), holding that in the context of approving NDAs, the FDA was "required only to ensure that a new drug applicant submitted either a list of patents claiming its drug or a declaration that there are no patents to be listed," irrespective of the accuracy or completeness of that information. App., infra, at 21. The court then struggled to place a similar interpretation on subsection (e)(4), recognizing the difficulty of doing so because (e)(4) applies to withdrawal of applications that had already been approved, and that in the context of that subsection the NDA holder's "failure to file the required information" logically "must mean that the NDA holder has failed to list some specific patent that is eligible for listing." Id. at 21-22.

To avoid that clear reading of the statute, the court fastened on a secondary transitional provision in subsection (c)(2) which required drug companies whose NDAs were approved before the passage of the Hatch-Waxman Act to identify eligible patents within thirty days after enactment. The court then held that subsection (e)(4) applied *only* to this narrow transitional obligation that existed until September 24, 1984, but not to the broader ongoing obligation of NDA holders under subsection (c)(2) to identify eligible patents, and that in this context, the agency had only a ministerial role to ensure literal compliance with the statute:

> We think it likely that in drafting subsection (e)(4), Congress intended to provide the FDA with a means to insure that holders of NDAs approved prior to the Act's passage would comply with the new patent listing

> requirements." Accordingly, we conclude that . . . the "failure to file the required patent information" discussed in subsection (e)(4) can reasonably be read to mean that the pioneer drug company has failed to submit a list of patents claiming the drug or a declaration that there are no patents to be issued.

App., infra, at 22-23.

The court of appeals candidly acknowledged that its holding left aaiPharma without a remedy to enforce "benefits conferred by Congress," app., infra, at 27, and that "if there is no enforcement mechanism to ensure that an NDA holder complies with its statutory obligations, an NDA holder can abuse the Orange Book listing process in such a way that . . . a third party patentee (a person or entity other than the pioneer drug company that holds a patent claiming a pioneer drug) fails to receive the protection of the stay even though it is entitled to receive that protection." Id. at 14. However, the court defended this result by holding that the statute itself created an "enforcement gap" (even though that "gap" was purely a creation of the court's refusal to accept the plain meaning of subsection (e)(4)); that "an agency's failure to fill an enforcement gap created by a statute is [not] necessarily arbitrary and capricious;" and that the FDA's explanation that it lacked the resources and expertise to police the listing process satisfied the requirement of reasoned agency decision making set forth in Motor Vehicle Mfrs. Ass'n of the United States v. State Farm Mutual Auto Ins. Co., 463 U.S. 29, 43 (1983). App., infra, at 25, 27-28.

On September 9, 2002, aaiPharma's Petition for Rehearing with Petition for Rehearing En Banc was denied.

REASONS FOR GRANTING THE PETITION

I. AN AGENCY'S REGULATION THAT LEAVES A PARTY WITHOUT A REMEDY TO ENFORCE A CLEAR STATUTORY RIGHT, AND MAKES THAT RIGHT SUBJECT TO THE UNREVIEWABLE CONTROL OF ANOTHER PRIVATE PARTY, IS UNREASONABLE UNDER STEP TWO OF CHEVRON

Under Chevron, if a "statute is silent or ambiguous with respect to the specific issue, the question ... is whether the agency's [interpretation] is based on a permissible construction of the statute." 467 U.S. at 843; Food and Drug Admin. v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 132 (2000). This Court and the courts of appeal have not hesitated to strike down agency rules and regulations that were not based on permissible constructions of their controlling statutes. E.g., AT&T Corp. v. Iowa Util. Board, 525 U.S. 366, 392 (1999) (discussed infra at 17); Kidney Ctr. v. Shalala, 133 F.3d 78, 87-88 (D.C. Cir. 1988) (vacating Medicare regulation capping provider reimbursement for bad debt because it relied upon an arbitrary construction of empowering statute). Here, the FDA regulation upheld by the court of appeals was not based on a permissible construction of the Hatch-Waxman Act, because it violates two principles of jurisprudence long recognized by this Court and the courts of appeal: that there must be a remedy to enforce every violation of a right conferred by Congress; and that a party's statutory rights cannot be made subject to the unreviewable control of another private party.

That a remedy must exist for every violation of a right has been axiomatic since the early days of this Court. In Marbury v. Madison, 1 Cranch 137, 163 (1803), this Court held that:

> The very essence of civil liberty certainly consists in the right of every individual to

> claim the protection of the laws, whenever he receives an injury. One of the first duties of government is to afford that protection.... The government of the United States has been emphatically termed a government of laws, and not of men. It will certainly cease to deserve this high appellation, if the laws furnish no remedy for the violation of a vested legal right.

This Court has consistently reaffirmed this doctrine through the years. E.g., Kendall v. United States ex rel. Stokes, 12 Pet. 524, 624 (1838) ("...the power to enforce the performance of the act must rest somewhere, or it will present a case which has often been said to involve a monstrous absurdity in a well-organized government, that there should be no remedy, although a clear and undeniable right should be shown to exist"); Peck v. Jenness, 48 U.S. 612, 623 (1849) ("A legal right without a remedy would be an anomaly in the law."); De Lima v. Bidwell, 182 U.S. 1, 176-77 (1901)("If there be an admitted wrong, the courts will look far to supply an adequate remedy"); Merrill Lynch, Pierce, Fenner & Smith, Inc. v. Curran, 456 U.S. 353, 376 (1982)("A duty declared by Congress does not evaporate for want of a formulated sanction.").[4]

The court of appeals' holding directly offends these authorities and the cardinal precept on which they rest. As the court readily acknowledged, it is "clear" that if the '853 patent met the eligibility criteria under § 355(c)(2), then aaiPharma had an absolute right under the Hatch-Waxman Act to have that patent identified by Lilly and listed by the FDA in the Orange Book, and to obtain a thirty-month stay

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[4]Although the principle that a remedy must exist for the violation of a right often arises in cases implying a private right of action, it is of equal force here where there is no private right of action and therefore, the only possible remedy for violation of aaiPharma's statutory rights is government enforcement.

against approval of ANDAs for generic versions of Prozac® by filing suit for infringement. App., infra, at 14, 26. It is equally clear that because aaiPharma had no private right of action under the FDA Act against Lilly, 21 U.S.C. § 337(a) ("all proceedings for the enforcement, or to restrain violations, of this chapter shall be by and in the name of the United States"), aaiPharma's only meaningful remedy for being deprived of its Hatch-Waxman rights was for the FDA to enforce the statute against Lilly. Although admitting that this proposition was "plausible" and had "some force," App., infra, at 27, the court of appeals nevertheless reached the opposite conclusion – that the government had no such duty, even if that meant aaiPharma had no remedy and its Hatch-Waxman rights were effectively nullified. When an agency's interpretation of a statute leaves a party with no remedy for a violation of its rights under that statute, such an interpretation cannot be "permissible" under step two of Chevron, and the court of appeals' decision cannot stand.[5]

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[5]It is of course no answer, as the court of appeals suggested, that "the third-party patentee can still pursue patent infringement suits against generic manufacturers." App., infra, at 26, n 7. Obviously Congress was aware of such suits when it provided for a thirty-month stay in the Hatch-Waxman Act, and must have believed that the additional right to such a stay was essential to protect the interests of patent owners. The court of appeals' holding thus deprives aaiPharma of a right deemed sufficiently important by Congress as to warrant inclusion in a federal statute. Similarly unpersuasive is the court's discussion of supposed antitrust remedies. Id. at 28, n 8. Both the court's discussion and the case cited, In re Buspirone Patent Litig., 185 F.Supp. 2d 363 (S.D.N.Y. 2002), concern overlisting by NDA holders of their own patents, not the circumstance involved here where an NDA holder *fails* to identify a third-party patentee's patent. Moreover, even assuming *arguendo* an antitrust case could be brought for failure to identify a patent, antitrust cases involve numerous elements of proof, including relevant market and monopoly power, and a court is not required to grant preliminary injunctive relief. The thirty-month stay, in contrast, is automatic.

This Court and the courts of appeal also have long recognized that rights determined by a federal statute cannot be made subject to the unreviewable discretion of private parties. In AT&T Corp. v. Iowa Utilities Board, 525 U.S. 366 (1999), this Court found an FCC rule unreasonable under step two of Chevron in part because it allowed new entrants to local telephone markets, rather than the Commission, power to determine which network elements incumbent carriers were required to provide to the entrants under the Telecommunications Act of 1996. Criticizing the FCC's failure to consider the availability of elements outside an incumbent's network in determining whether access to the incumbent's elements was "necessary" and would "impair" an entrant's ability to provide services, the Court held that "[the Commission's] judgment allows entrants, rather than the Commission, to determine whether access to proprietary elements is necessary, and whether the failure to obtain access to nonproprietary elements would impair the ability to provide services." Id at 389; see also A.L.A. Schechter Poultry Corp. v. United States, 295 U.S. 495, 537 (1935) (observing that Congress could not delegate legislative authority to trade or industrial associations because it would be "unknown to our law" and "utterly inconsistent with the constitutional prerogatives and duties of Congress"); Perot v. Fed. Election Comm'n, 97 F.3d 553, 559 (D.C. Cir. 1996) ("We agree with the general proposition that when Congress has specifically vested an agency with the authority to administer a statute, it may not shift that responsibility to a private actor...."); Sierra Club v. Sigler, 695 F.2d 957, 962 fn 3 (5th Cir. 1983) ("an agency may not delegate its public duties to private entities, particularly private entities whose objectivity may be questioned...."). At a minimum, the private party's conduct must remain subject to the "active" and "meaningful" final reviewing authority of the agency. Assinibone and Sioux Tribes v. Board of Oil and Gas Conservation, 792 F.2d, 795 (9th Cir. 1986) (agency must retain "meaningful independent

review"); Sierra Club v. Lynn, 502 F.2d, 43, 59 (5th Cir. 1974) (agency must "independently perform its reviewing, analytical, and judgment functions and participate actively and significantly").[6]

Here, as in AT&T, the FDA's regulation allows NDA holders, rather than the agency, to determine whether third-party patentees receive the protections of the thirty-month stay.[7] Indeed, the court of appeals conceded that the effect of its giving deference to the FDA's regulation was that a self-interested private party (the NDA holder) could "abuse" the FDA regulatory process set forth in the statute so as to deprive another private party (the patent owner) of its clear statutory rights: "If there is no enforcement mechanism to ensure that an NDA holder complies with its statutory obligations, an NDA holder can abuse the Orange

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[6]The court of appeals attempted to avoid this problem by reasoning that because Congress did not impose any duty on the FDA to enforce the patent listing requirements of the Hatch-Waxman Act, then the FDA necessarily did not unlawfully delegate any such duty to NDA holders. App., infra, at 25. However, that justification is circular, and merely begs the question whether the FDA had the duty in the first place. The court of appeals answered that question incorrectly. It was able to conclude that the FDA had no "duty" only (1) by reading the duty out of the statute despite its plain meaning (see supra at 11) and (2) by adopting a construction of the statute that was manifestly unreasonable because it left aaiPharma without a remedy for a violation of its statutory rights and made those rights subject to the whim of another self-interested private party. (See supra at 13).

[7]The court of appeals failed to recognize that there is not necessarily a commonality of interest between an NDA holder and a third-party patentee where the NDA holder is given full control, contrary to the statute, in deciding whether to identify a patent to the FDA for Orange Book listing. Whether the value of the patent owner's intellectual property is protected is of no concern to the NDA holder, particularly if the NDA holder has not licensed the patent.

Book listing process in such a way that...a third party patentee...fails to receive the protection of the stay even though it is entitled to receive that protection." App., infra, at 14. The court of appeals' holding -- that a regulation allowing such "abuse" by an interested private party rested on a permissible construction of the Hatch-Waxman Act -- thus squarely conflicts with the decisions of this Court and the other courts of appeal.

II. THE COURT OF APPEALS' DISREGARD OF PLAIN STATUTORY LANGUAGE CONFLICTS WITH THIS COURT'S PRECEDENT

Not only did the court of appeals validate an FDA regulation that eviscerates an acknowledged statutory right, it justified its conclusion by utilizing Chevron step-two deference because it wrongly perceived internal inconsistency, and hence ambiguity, in the statute. No such ambiguity can be found in the plain language of the Hatch-Waxman Act. The court of appeals' departure from Chevron step-one and refusal to implement the manifest intent of Congress violate established and important rules of administrative law and statutory construction.

"If the intent of Congress is clear, that is the end of the matter: for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." Chevron, 467 U.S. at 843. The Court has followed this bedrock principle of administrative law in an unbroken line of cases after Chevron, underscoring that the plain meaning of statutory language supplies that unambiguous congressional intent. INS v. Cardoza - Fonseca, 480 U.S. 421, 431 (1987) (court "bound to 'assume "that the legislative purpose is expressed by the ordinary meaning of the words used."'") (citations omitted); Cowart v. Nicklos Drilling, 505 U.S. 469, 475 (1992) ("the beginning point must be the language of the statute, and when the statute speaks with clarity to an issue judicial inquiry into the statute's meaning, in all but the most extraordinary circumstance, is finished");

Barnhart v. Sigmon Coal Co., Inc., 534 U.S. 438, 461-62 (2002) ("We have stated time and again that courts must presume that a legislature says in a statute what it means and means in a statute what it says there. When the words of a statue are unambiguous, then, this first canon is also the last: judicial inquiry is complete.").

The court of appeals acknowledged that, "considered in isolation," subsection (e)(4)'s command that the FDA, after notice and opportunity for hearing, "shall . . . withdraw approval of a [previously approved NDA]" if it finds that the NDA holder did not timely identify the required patent information "could arguably qualify as [a] clear expression [] of congressional intent about the proper role of the FDA in Orange Book listing disputes."[8] App., infra at 19. It drew the same conclusion in regard to that part of subsection (c)(2) requiring that the FDA "shall publish" the patent information specified by an NDA holder, but found that this sentence in subsection (c)(2) and subsection (e)(4), when read together, "appear to conflict." App., infra, at 19. The "conflict" arose from the court's perception that (e)(4) envisioned an active enforcement role for the FDA, while (c)(2) mandated a passive, or "ministerial role." The court of appeals therefore proceeded to step two of Chevron because it "conclude[d] that Congress has failed to express clearly its intent about the FDA's role in the Orange Book listing process." App., infra, at 19.

This reasoning was fundamentally flawed in several respects. To begin with, there is plainly no conflict between a purely "ministerial" FDA role under subsection (c)(2) in the case of eligible patents actually identified by an NDA holder, and a substantive, enforcement role in the very different context addressed by subsection (e)(4) -- where an NDA holder has failed to identify eligible patent

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[8]This acknowledgement also extended to the command of subsection (d)(6) that FDA "shall issue an order refusing to approve" a pending NDA if it failed to include the required patent information. App., infra,, at 19.

information for Orange Book publication. The "conflict" results only from the court's unfounded assumption that the FDA's role must be the same - always active or always passive - with respect to all Orange Book listing disputes, irrespective whether the dispute arises (i) from the NDA holder's identification of an ineligible patent, or (ii) from the NDA holder's failure to identify an eligible patent for listing. This is far different from a conflict that would render an otherwise clear command ambiguous under Chevron step one. Subsection (e)(4)'s directive that the FDA "shall withdraw" approval of an NDA if its holder fails timely to submit required patent information can only truly result in conflict under Chevron if some other provision directs the FDA not to withdraw NDA approval under these circumstances. No such countermanding provision exists in the Hatch-Waxman Act.

The court of appeals' assumption that the FDA must be always active or passive finds no support in the text of the statute, or its legislative history, and this Court in similar circumstances has cautioned against taking liberties with statutory language to address alleged strain between statutory provisions or to support policy-based interpretations. NLRB v. Health Care and Retirement Corp. of America, 511 U.S. 571, 581 (1994) ("there may be some tension between two provisions in the act, but we find no authority for suggesting that that tension can be resolved by distorting the statutory language . . ."); NLRB v. Kentucky River Community Care, Inc., 532 U.S. 706, 720 (2001) ("the problem with the argument is not the soundness of (agency) policy... It is that the policy cannot be given effect

through this statutory text").[9] Indeed, the D.C. Circuit previously has found a different FDA Hatch-Waxman

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[9]In not only departing from the plain meaning of the statute and Chevron step-one analysis, but also resting its conclusions on public policy judgments about the desirability of a uniform FDA role, the court of appeals further invaded the legislative realm. See MCI Telecomm. Corp. v. AT&T, 512 U.S. 218, 234 (1994) (a federal agency's "estimations, of desirable policy cannot alter the meaning [of a statute]."). The court of appeals stated the principle behind its policy-making efforts, explaining in a footnote "that if the FDA has a duty to police improper refusal to list patents, it *must* also have a duty to police improper listings of patents." App. infra, at 17 n 6 (emphasis supplied). The court later elaborated:

> We think it clear that if Congress had intended to impose any duty on the FDA to police Orange Book listing, it would have required the FDA to ensure that ineligible patents are not listed in the Orange Book. This is because . . . improper listing of patents in the Orange Book is a *far more serious problem* than the improper refusal to list patents . . . . As a result, we find it hard to believe that Congress would impose a duty on the FDA to police the improper refusal to list patents without also imposing a duty to police the improper listing of patents.

App., infra, at 23-24 (emphasis supplied).

The court of appeals did not specify any source for its policy judgment that improper listing is "a far more serious problem" than failing to list. Rather than deriving it from the language of the statute or any other indication of congressional intent, the court of appeals based its policy judgment solely on its independent assessment that the rights of those seeking to sell generic drugs were more important than the rights of patent owners, even though that judgment effectively eliminated rights clearly granted to patent owners under the statute. Moreover, improper listing is not necessarily a "more serious" problem than failing to list. The

regulation to be a policy-driven departure from a clear statutory command. See Mova Pharm. Corp. v. Shalala, 140 F.3d 1060, 1069 (D.C. Cir. 1998) (concluding under Chevron step-one that "the FDA's successful defense requirement is inconsistent with the unambiguously expressed intent of Congress" . . . and "gravely inconsistent with the text and structure of the statute").[10]

Second, the court of appeals' premise for finding a "conflict" - that the FDA's role in listing patents identified by an NDA holder under subsection (c)(2) is purely "ministerial" - is incorrect. The antecedent to the command that the FDA "shall publish" is the "patent information [submitted by the NDA holder] under this subsection" namely: information about "any patent which claims the drug for which the [NDA] was submitted . . . and with respect to which a claim of infringement could reasonably be asserted [against an unlicensed user]." 21 U.S.C. § 355(c)(2) The natural reading of the provision as a whole is that the FDA must list in the Orange Book only those patents identified by an NDA holder that in fact satisfy the eligibility criteria specified by Congress. See Pfizer, Inc. v. FDA, 753 F.Supp. 171, 174 (D.Md. 1990) (FDA refused, based on its interpretation of subsections (b)(1) and (c)(2), to publish in the Orange Book information about a patent

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former results only in pre-marketing litigation of infringement issues which is fully consistent with the objectives of the Hatch-Waxman Act, while the latter -- if there is no enforcement remedy, as the court of appeals held -- results in a patent owner's irrevocably losing its statutory rights.

[10]Compounding this disregard of plain statutory language, it is worthy of note that the particular statutory interpretation the court of appeals advanced in its decision was not even advanced by the FDA itself in promulgation of the regulation at issue or in its brief to the court of appeals.

submitted by Pfizer).[11] At a minimum, the plain language of subsection (c)(2) clearly does not mandate a purely ministerial role for the FDA. The only way to sustain such a role, therefore, would be to find such an interpretation permissible under step two of Chevron. A ministerial role under subsection (c)(2) resulting from the agency's interpretation of the statute cannot be viewed as a congressional prescription that conflicts with or countermands the clear command of subsection (e)(4) requiring FDA enforcement when an NDA holder fails to identify an eligible patent. Only clear statutory language can produce the "conflict" required to find ambiguity under Chevron. Moreover, as a corollary to this principle, to the extent the FDA's interpretation of its role under subsection (c)(2) were construed to conflict with the plain statutory language of subsection (e)(4), then that interpretation necessarily could not be reasonable.

Finally, when the entirety of subsection (c)(2), and not just the sentence isolated from context by the court of appeals, is read together with subsection (e)(4), the provisions clearly fit together as part of a harmonious whole. Subsection (c)(2) requires NDA holders to identify eligible patents, and subsection (e)(4) is an enforcement mechanism to ensure that they do so. These complementary provisions achieve the congressional goal of complete and proper patent listing – neither under- nor over-inclusion –

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[11] Although some courts of appeal have noted in passing that the FDA has taken a ministerial role in listing decisions, no circuit court (other than the Fourth Circuit in this case) has done so in the context of a dispute concerning the propriety of that role. See e.g. Andrx Pharm., Inc. v. Biovail Corp., 276 F.3d 1368, 1377-78 (Fed. Cir. 2002) (noting without comment that under 21 C.F.R. § 314.53, the FDA declines to review submitted patent information); American Bioscience, Inc. v. Thompson, 269 F.3d 1077, 1084 (D.C. Cir. 2001) (noting that the parties had agreed that the FDA's role was ministerial); Mylan Pharm., 268 F.3d at 1329 (noting without comment the FDA's characterization of its role as ministerial in the district court proceeding).

and also guarantee that similarly situated patent owners are not treated differently (one able to obtain the thirty-month stay, one not) at the whim of an NDA holder. See American Bioscience, Inc. v. Thomson, 269 F.3d 1077 (D.C. Cir. 2001) (NDA holder chose to identify third-party patentee's patent; court vacated FDA's approval of an ANDA for a drug covered by that patent).

In contrast, the court of appeals' attempted reconciliation of subsections (c)(2) and (e)(4),[12] see supra at 11, results in both incomplete listing of patents and unequal treatment. Indeed, the only "goal" realized by the court of appeals is to ensure that the FDA, the agency authorized to administer and enforce the Hatch-Waxman Act, instead has a trivial role in all patent listing situations: publishing all patents identified by NDA holders even if they do not meet the eligibility criteria under (c)(2); ensuring only that an NDA applicant furnishes a list of patents under (d)(6), even if the list is inaccurate; ensuring only that previously-approved NDA holders furnished a list of patents in 1984 under (e)(4), even if that list was inaccurate; and having no say when an NDA holder refuses to list an eligible patent. Such a regime cannot possibly be what Congress envisioned, and it achieves a superficial consistency at the price of eviscerating the statute.

The court of appeals' holding thus rests on an unacceptable failure to apply step one of Chevron, and review is appropriate to correct its disregard for the intent of Congress evidenced by the plain meaning of subsection (e)(4).

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[12]That the court undertook this reconciliation effort stands in curious contrast to its conclusion that irreconcilable statutory conflict required departure from Chevron step one in the first instance.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted,

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Filed: August 5, 2002

UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT

No. 01-2113
(CA-01-152-F)

aaiPharma Incorporated,

Plaintiff - Appellant,

versus

Tommy G. Thompson, etc., et al.,

Defendants - Appellees.

O R D E R

The court amends its opinion filed July 10, 2002, as follows:

On page 21, first full paragraph, line 19 -- "FTC" is corrected to read "FDA."

For the Court - By Direction

/s/ Patricia S. Connor
Clerk

PUBLISHED

UNITED STATES COURT OF APPEALS

FOR THE FOURTH CIRCUIT

AAIPHARMA INCORPORATED,
Plaintiff-Appellant,

v.

TOMMY G. THOMPSON, Secretary of Health and Human Services; BERNARD SCHWETZ, DVM, Ph.D., Acting Commissioner of the UnitedNo. 01-2113 States Food and Drug Administration; UNITED STATES FOOD AND DRUG ADMINISTRATION,
Defendants-Appellees,

BARR LABORATORIES, INCORPORATED; PHARMACEUTICAL, INCORPORATED,
Intervenors.

Appeal from the United States District Court for the Eastern District of North Carolina, at Wilmington. James C. Fox, Senior District Judge.
(CA-01-152-F)

Argued: February 25, 2002

Decided: July 10, 2002

Filed: July 10, 2002

Before MICHAEL, Circuit Judge, Raymond A. JACKSON,

United States District Judge for the Eastern District of Virginia, sitting by designation, and Jerome B. FRIEDMAN,

United States District Judge for the Eastern District of Virginia, sitting by designation.

Affirmed by published opinion. Judge Michael wrote the opinion, in which Judge Jackson and Judge Friedman joined.

COUNSEL

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OPINION
MICHAEL, Circuit Judge:

The Federal Food, Drug, and Cosmetic Act (FFDCA) requires the manufacturer of a brand name drug approved by the Food and Drug Administration (FDA) to provide the FDA with a listing of all patents that claim the approved drug or a method of using the drug. See 21 U.S.C. § 355 (b)(1), (c)(2). The FDA publishes these listings in its Approved Drug Products With Therapeutic Equivalence Evaluations, a publication commonly known as the Orange Book. The plaintiff, aaiPharma Inc., has sued the FDA, contending that the agency has a duty to ensure the accuracy of Orange Book listings and that the agency's refusal to do so violates the Administrative Procedure Act (APA). The district court rejected aaiPharma's APA challenge, concluding that the FFDCA assigns the FDA a purely ministerial role regarding Orange Book listings. We affirm.

I.

Orange Book listings play an important role in the statutory and regulatory framework created by the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. §§ 355, 360cc and 35 U.S.C. §§ 156, 271, 282), commonly known as the Hatch-Waxman Act (Hatch-Waxman or the Act). Hatch-Waxman amended both the FFDCA and the patent laws in an effort to strike a balance between "two conflicting policy objectives: to induce name-brand pharmaceutical firms to make the investments necessary to research and develop new drug products, while simultaneously enabling competitors to bring cheaper, generic copies of those drugs to market." Abbott Labs. v. Young, 920 F.2d 984, 991 (D.C. Cir. 1990) (Edwards, J., dissenting on other grounds).

Prior to Hatch-Waxman's passage in 1984, both pioneer (brand name) and generic drug manufacturers who wished to bring a drug to market were required to file a New Drug Application (NDA) with the FDA. This requirement posed a formidable barrier to market entry for generic drug companies because preparation of an NDA requires expensive clinical studies demonstrating the proposed drug's safety and effectiveness. In addition, a generic manufacturer could not begin the necessary research and clinical studies until any patents on the brand name drug it sought to copy had expired because its research efforts would have infringed the patents held by the pioneer drug company. This meant that a pioneer drug company's monopoly on its brand name drug was effectively extended to include not only the terms of any patents on the brand name drug, but also the time it took generic competitors to complete the NDA process after these patents had expired. Hatch-Waxman addressed these problems by creating a streamlined procedure for FDA approval of generic drugs. A drug company that wishes to market a generic version of a brand name drug may now submit an Abbreviated New Drug Application (ANDA) to the FDA. See 21 U.S.C. § 355(j). By filing an ANDA, a generic manufacturer can rely on the clinical studies performed by the pioneer drug manufacturer and is not required to prove the safety and effectiveness of its generic drug from scratch. Instead, the generic manufacturer must prove only that its drug is bioequivalent to the brand name drug it wants to copy. See id. § 355(j)(2)(A). In addition, Hatch-Waxman amended the patent laws so that a generic drug manufacturer no longer infringes the patents on a brand name drug by performing acts necessary to prepare an ANDA. See 35 U.S.C. § 271(e)(1).

Hatch-Waxman also contains a complex set of provisions designed to protect the intellectual property rights of pioneer drug companies and others holding patents on brand name drugs. The Act requires each drug

company filing an NDA to include in its application a list of all the patents that "claim[ ] the drug for which the applicant submitted the application or which claim[ ] a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." 21 U.S.C. § 355(b)(1). If the FDA approves the application, the agency is required to publish this list in the Orange Book.[1] An NDA applicant must also amend its application to include information about any new patents claiming its drug that issue while the NDA is pending. Id. In addition, the holder of an approved NDA is required to submit to the FDA for Orange Book listing any new patents that claim the approved drug within thirty days of their issuance. Id. § 355(c)(2). With respect to each patent listed in the Orange Book for a pioneer drug, an ANDA applicant seeking to copy that drug must make one of the following four certifications in its initial application for FDA approval: (I) that no patent information for the pioneer drug has been submitted to the FDA (a "paragraph I certification"), (II) that the patent has expired (a "paragraph II certification"), (III) that the patent will expire on a specific date (a "paragraph III certification"), or (IV) that the patent "is invalid or will not be infringed by the manufacture, use, or sale of the new drug" for which the ANDA applicant seeks approval (a "paragraph IV certification"). Id. § 355(j)(2)(A)(vii)(I)-(IV). An ANDA applicant must also make an additional certification as to any new patent listed in the Orange Book while its application is pending, so long as the NDA holder submits the new patent to the FDA for listing no more than thirty days after the patent's issuance. 21 C.F.R. §

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[1] For ease of reference, we will refer to those patents that meet the statutory criteria for Orange Book listing with respect to a given drug as patents that claim the drug. We need not explain the statutory criteria in any detail, but the general idea is that a patent claims a drug under 21 U.S.C. § 355(b)(1) if the patent might be infringed by a generic version of that drug.

314.94(a)(12)(vi). The certification made by the ANDA applicant determines the date on which FDA approval of the application can become effective. ANDAs containing paragraph I or II certifications may be approved immediately if the FDA finds that all the relevant scientific and regulatory requirements have been met. 21 U.S.C. § 355(j)(5)(B)(i). An ANDA that contains a paragraph III certification becomes effective on the patent's expiration date, assuming that other FDA requirements have been satisfied. Id. § 355(j)(5)(B)(ii). Thus, certifications under paragraphs I, II, and III tell the FDA that it need not worry about the patent law implications of the generic drug because the drug will not enter the market until any relevant patents have expired. In contrast, an ANDA applicant making a paragraph IV certification intends to market its product before the relevant patents have expired. The effective date for an ANDA containing a paragraph IV certification is determined by the outcome of the following sequence of events.

An ANDA applicant making a paragraph IV certification with respect to a patent must give notice of this certification to both the NDA holder and the patent holder (often, but not always, these will be the same party) and must explain in detail why it believes that the patent is invalid or will not be infringed by the generic drug for which it seeks approval. Id. § 355(j)(2)(B). Hatch-Waxman provides that the act of filing a paragraph IV certification with respect to a patent creates a cause of action for patent infringement in the patent holder. See 35 U.S.C. § 271(e)(2)(A) ("It shall be an act of infringement to submit . . . [an ANDA] . . . if the purpose of such submission is to obtain [FDA] approval . . . to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent . . . before the expiration of such patent."). Once the patent holder receives notice of the certification, it has forty-five days in which to file a suit for patent infringement. Failure to file within this forty-five day period means that the FDA

may approve the ANDA without delay. 21 U.S.C. § 355(j)(5)(B)(iii). But if the patent holder files suit, FDA approval of the ANDA is automatically stayed for up to thirty months.[2] Together, these provisions protect the holder of a patent that claims a brand name drug by giving the patent holder a chance to vindicate its intellectual property rights before the FDA approves a generic version of the drug. See Bristol-Myers Squibb Co. v. Royce Labs., Inc., 69 F.3d 1130, 1135 (Fed. Cir. 1995). Orange Book listing of a patent is important because it is the trigger for this protection. If a patent is not listed in the Orange Book, ANDA applicants do not have to file a paragraph IV certification, and the patent holder is unable to take advantage of the thirty-month stay.

II.

On July 10, 2001, aaiPharma received a patent (the '853 patent) on a polymorphic variant of the active ingredient in Prozac, a widely prescribed antidepressant drug manufactured by Eli Lilly & Company (Lilly). U.S. Patent No. 6,258,853. Lilly's claim of exclusivity for Prozac under the patent laws was scheduled to expire on August 2, 2001. Several generic drug manufacturers (including intervenors Barr Laboratories, Inc. and Par Pharmaceuticals, Inc.) were set to begin marketing generic versions of Prozac the next day. aaiPharma was concerned that its new patent might be infringed by these generic drugs, and the company therefore sought to have its '853 patent included in the Orange Book listing for Prozac. As explained above, Orange

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[2] More precisely, the stay continues until the earliest of (1) the expiration of the patent, (2) judicial resolution of the patent infringement suit, or (3) thirty months from the patent holder's receipt of notice. 21 U.S.C. § 355(j)(5)(B)(iii). In addition, a court in which a patent suit is pending may order a shorter or longer stay if "either party to the action fail[s] to reasonably cooperate in expediting the action." Id.

Book listing of the '853 patent would confer significant benefits on aaiPharma. An ANDA applicant seeking to market a generic version of Prozac before the expiration of the '853 patent would be required to make a paragraph IV certification regarding the patent. aaiPharma would then have the ability to trigger the thirty-month stay (and so delay FDA approval of the ANDA applicant's generic version of Prozac) by filing a patent infringement suit against the applicant.[3]

Because only the NDA holder can submit patents claiming its approved drug for listing in the Orange Book, aaiPharma asked Lilly to submit the '853 patent to the FDA. Lilly refused.[4] aaiPharma then sent a letter to the FDA asking the agency to "contact Lilly to confirm the correctness of Lilly's omission of information about the '853 patent from the list of Prozac-related patents in the Orange Book." aaiPharma suggested that if Lilly persisted in its refusal to list the '853 patent, the FDA had an obligation to intervene. The FDA, however, has determined that it will not become an arbiter of the correctness of Orange Book listings. Its regulations implementing the Hatch-Waxman Act provide only a very limited mechanism for resolving disputes regarding those listings. See 21 C.F.R. § 314.53(f). Consistent with its regulation, the FDA responded to aaiPharma's request by sending a letter to Lilly requesting that Lilly confirm the correctness of its Orange Book listing for Prozac.

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[3] As the district court observed, aaiPharma does not have a drug of its own ready for market. The record does not disclose the reasons for aaiPharma's avid interest in securing the thirty-month stay. We decline to speculate about aaiPharma's motives as they are not material to the resolution of this case.

[4] Lilly would have benefitted significantly from any delay in the introduction of generic Prozac, and so it had a strong financial incentive to grant aaiPharma's request that the '853 patent be listed in the Orange Book. There is nothing in the record to indicate why Lilly refused aaiPharma's request despite this financial incentive.

The letter explained that the FDA would make no change to the listing unless Lilly asked it to do so. The record does not indicate whether Lilly has responded to this letter.

Having failed in its efforts to secure Orange Book listing for the '853 patent by contacting Lilly and the FDA, aaiPharma brought this lawsuit under the Administrative Procedure Act in the Eastern District of North Carolina on August 2, 2001, only hours before the FDA was set to approve the marketing of several generic versions of Prozac. aaiPharma alleged that the FDA's failure to require Lilly to list the '853 patent in the Orange Book was "arbitrary, capricious . . . or otherwise not in accordance with law" under § 706(2)(A) of the APA and asked the court to order the FDA to require Lilly to submit the '853 patent for listing in the Orange Book. aaiPharma also filed a motion for preliminary relief under Fed. R. Civ. P. 65. It sought a temporary restraining order and a preliminary injunction that would prevent the FDA from approving any ANDAs for generic Prozac until the court could determine whether the FDA had a duty to require the listing of the '853 patent. The district court held a non-evidentiary hearing on August 2, 2001, and denied the motion for preliminary relief from the bench. In a subsequent opinion dated August 13, 2001, the court explained that it had denied aaiPharma's request for preliminary relief primarily on the ground that there was no likelihood of success on the merits because the FDA's interpretation of the relevant statutes was not only reasonable, but correct. See Blackwelder Furniture Co. of Statesville, Inc. v. Seilig Mfg. Co., 550 F.2d 189, 195 n.3 (4th Cir. 1977) (stating that the probability of success on the merits is the most important factor in evaluating a motion for a preliminary injunction when there is no decided imbalance of hardship in the plaintiff's favor if the injunction is denied). The court reasoned that Hatch-Waxman places the responsibility for deciding which patents to list in the Orange Book solely on NDA holders like Lilly and that the FDA's role in Orange Book listings is

purely ministerial: "Congress decided that the FDA's task simply is to publish without question whatever patent information . . . is supplied to it by the NDA holder pursuant to the statute." Although the court had given no notice to the parties of any intention to enter final judgment in the case, the court noted in the conclusion of its opinion that it was "effectively . . . ruling against [aaiPharma] `on the merits.'" The court therefore directed the clerk "to enter judgment and to close [the] file." aaiPharma appeals on both procedural and substantive grounds. Specifically, it contends that the district court erred procedurally by entering a final judgment on the merits without providing aaiPharma with notice and an adequate opportunity to be heard and that the court erred substantively by upholding the FDA's policy of non-intervention in Orange Book listing disputes.

III.

We first address the procedural question of whether the district court, after holding a hearing on aaiPharma's motion for preliminary relief, erred by entering judgment against the company without giving notice that it was considering final disposition on the merits. Although Fed. R. Civ. P. 65(a)(2) allows a district court to order consolidation of a preliminary injunction hearing with a trial on the merits, we have long held that before consolidation is ordered, "the parties should normally receive clear and unambiguous notice to that effect either before the hearing commences or at a time which will still afford the parties a full opportunity to present their respective cases." Gellman v. Maryland, 538 F.2d 603, 604 (4th Cir. 1976) (internal quotation marks and citation omitted). The notice requirement is necessary because "`the facts adduced [at a preliminary injunction hearing] often will not be sufficient to permit an informed determination of whether a direction for the entry of judgment is appropriate.'" Berry v. Bean, 796

F.2d 713, 719 (4th Cir. 1986) (quoting 11 Charles Alan Wright & Arthur R. Miller, Federal Practice and Procedure S 2950 at 492 (1973)). As a result, "a party addressing only issues of preliminary relief should not ordinarily be bound by its abbreviated and only partially informed presentation of the merits." Id. Here, the district court gave the parties no notice of any kind that it might enter judgment on the merits after the hearing on the motion for preliminary relief. Although this case turns completely on legal issues, and aaiPharma has not pointed to any factual evidence that it might have presented to the district court, the company contends that it did not have the opportunity to present the district court with the full battery of legal arguments in favor of its position. Specifically, aaiPharma claims that if it had received notice that the district court intended to rule on the merits, it would have submitted further briefing addressing such issues as "the Hatch-Waxman Act's application to non-NDA holders [and] the mandatory nature of NDA holders' obligations under the Act to provide information on eligible patents to [the] FDA." Brief for Appellant at 20. We agree with aaiPharma that the district court's spontaneous entry of final judgment was error because it deprived aaiPharma of a full and fair opportunity to present its case. Cf. U. S. Dev. Corp. v. Peoples Fed. Sav. & Loan Ass'n, 873 F.2d 731, 736 (4th Cir. 1989) (stating that "regardless of a claim's merits, a district court may not sua sponte enter summary judgment against it until the claim's proponent has been given notice and a reasonable opportunity to be heard"). Ordinarily, the proper course would be to vacate the district court's judgment and to remand for that court to decide the merits of the case after the parties have had a fair chance to develop their positions.

In this case, however, special circumstances allow us to put aside the district court's procedural error and render a decision on the merits. First, aaiPharma acknowledges that it has now presented us with all the legal arguments that it would have made to the district court if given the

opportunity. Indeed, aaiPharma's counsel stated at oral argument that his client "would welcome" a decision on the merits from this court. This, we conclude, amounts to a waiver of aaiPharma's objection to the district court's procedural error. Second, the case turns wholly on the legal question of whether the FDA's refusal to police the correctness of Orange Book listings violates the APA. If we were to remand the case, we would likely find ourselves reviewing the district court's ruling on this issue next year in light of the same record and the same arguments we have before us now. Under these circumstances, we conclude that it is appropriate to reach the merits of the case. We therefore turn to the question of whether the FDA's refusal to conduct any independent inquiry into the correctness of Orange Book listings is arbitrary, capricious, or otherwise not in accordance with law.

IV.

Because Lilly's NDA for Prozac was approved long before aaiPharma obtained the '853 patent, 21 U.S.C. § 355(c)(2) determines Lilly's obligations with respect to that patent. It provides that for patents issued after the approval of an NDA, the NDA holder

> shall file with the [FDA] the patent number and the expiration date of any patent which claims the drug for which the application was submitted or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. . . . [I]f the [NDA holder] could not file [the required patent information as part of its application] because no patent had been issued when an application was filed or

> approved, the holder shall file [the required information regarding the new patent] not later than thirty days after the date the patent involved is issued. Upon the submission of patent information under this subsection, the [FDA] shall publish it.

21 U.S.C. § 355(c)(2). It is clear, then, that if (as aaiPharma asserts) the '853 patent "claims" Prozac in the sense provided in § 355(c)(2), Lilly is obligated to submit the '853 patent for listing in the Orange Book, and the FDA is required to publish the submitted listing.[5] It is unclear, however, whether there is any effective way to enforce an NDA holder's obligation to submit for Orange Book listing every patent that claims its approved drug (or its corresponding obligation not to submit patents that do not claim its approved drug).

The question is important because, as we explained earlier, listing of a patent in the Orange Book triggers the availability of the thirty-month stay. If there is no enforcement mechanism to ensure that an NDA holder complies with its statutory obligations, an NDA holder can abuse the Orange Book listing process in such a way that (1) the NDA holder enjoys the protection of the thirty-month stay when it is not entitled to do so, or (2) a third party patentee (a person or entity other than the pioneer drug company that holds a patent claiming a pioneer drug) fails to receive the protection of the stay even though it is entitled to receive that protection. The first (and more serious) problem arises when an NDA holder wrongly lists a patent in the Orange Book that does not actually claim its approved drug under the standard set forth in § 355(c)(2). Once the patent is listed, the NDA holder can delay an ANDA

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[5] We express no opinion, of course, on the question of whether the '853 patent meets the statutory criteria for inclusion in the Orange Book listing for Prozac.

applicant's entry into the marketplace for up to thirty months (and extend its monopoly power) simply by filing a patent infringement suit. The NDA holder receives this benefit regardless of whether the patent meets the statutory criteria for Orange Book listing. Thus, the absence of any mechanism for ensuring the accuracy of Orange Book listings means that "the patentee/NDA holder [can receive] almost automatic injunctive relief for even marginal infringement claims." Terry G. Mahn, Patenting Drug Products: Anticipating Hatch-Waxman Issues During the Claims Drafting Process, 54 Food Drug Cosm. L.J. 245, 250 (1999). The harm to generic drug manufacturers, and ultimately to the consuming public, is obvious. The second problem arises when an NDA holder refuses to submit an eligible third-party patent for listing in the Orange Book. This is the wrong complained of by aaiPharma. Although an improper refusal to list a patent in the Orange Book is less obviously threatening to the public interest than an improper listing of a patent, we agree with aaiPharma that third-party holders of patents claiming an approved drug are also entitled to the thirty-month stay. Accordingly, aaiPharma has a legitimate grievance if Lilly has wrongfully refused to list the '853 patent in the Orange Book.

We are not the first court to consider whether parties aggrieved by an NDA holder's Orange Book listings have any remedy. Generic drug manufacturers have brought suits against NDA holders to compel them to de-list certain patents on the ground that the patents did not claim the approved drug under the statutory criteria in §§ 355(b)(1) and (c)(2). It is now well established, however, that "a generic drug manufacturer cannot bring a declaratory judgment action or an injunctive action against a NDA holder under either the FFDCA or the patent laws requiring it to take steps to`delist' a patent from the Orange Book." Andrx Pharm., Inc. v. Biovail Corp., 276 F.3d 1368, 1373-74 (Fed. Cir. 2002). If a generic manufacturer cannot sue an NDA holder to compel delisting of a patent, it follows that a

third party patentee cannot sue an NDA holder to compel listing of a patent. This is why aaiPharma has brought suit against the FDA rather than against Lilly. The Federal Circuit, however, has acknowledged that a party aggrieved by an NDA holder's Orange Book listing could properly bring a lawsuit under the APA raising a challenge to the FDA's practice of "refusing to inquire into the correctness of [an Orange Book] listing." Id. at 1379 n.8. This is that case.

The FDA's policy regarding Orange Book listing disputes is codified in § 314.53(f) of the regulations implementing Hatch-Waxman:

> Correction of patent information errors. If any person disputes the accuracy or relevance of patent information submitted to the agency under this section and published by theFDA in the list [the Orange Book], or believes that an applicant has failed to submit required patent information, thatperson must first notify the agency in writing stating the grounds for disagreement. . . . The agency will then request of the applicable new drug application holder that the correctness of the patent information or omission of patent information be confirmed. Unless the application holder withdraws or amends its patent information in response to FDA's request, the agency will not change the patent information in the list.

21 C.F.R. § 314.53(f) (emphasis added). The regulation goes on to say that ANDA applicants must make a proper certification regarding each patent listed in the Orange Book "despite any disagreement as to the correctness of the patent information." Id. In short, the FDA's position is that if the NDA holder stands on its Orange Book listing, aggrieved parties are out of luck. The FDA defends this purely

ministerial conception of its role in the Orange Book listing process by explaining that it lacks both the resources and the expertise to police the correctness of Orange Book listings. aaiPharma acknowledges that the FDA has no responsibility to independently evaluate the correctness of every patent listing submitted by an NDA holder. It simply argues that if a party alerts the FDA to concerns that an NDA holder has incorrectly failed to list a patent, the FDA must do more than simply ask the NDA holder to look into the matter and accept whatever it says. Specifically, aaiPharma contends that upon learning of a dispute about the correctness of an Orange Book listing, "the FDA is required to make a substantive determination about eligibility and to take remedial measures against the NDA holder if it determines that the patent should be listed." Reply Brief for Appellant at 6 n.1. According to aaiPharma, the FDA's refusal to inquire into the correctness of Orange Book listings improperly delegates the FDA's statutory duties to NDA holders.[6]

In evaluating the FDA's interpretation of its governing statute, we employ the familiar two-step analysis established by the Supreme Court in Chevron U.S.A. Inc. v. Natural Res. Def. Council, Inc., 467 U.S. 837, 842-45 (1984). In step one of the Chevron analysis, we ask whether "Congress has directly spoken to the precise question at issue." Here, that question is whether the FDA has an

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[6] The parties frame the central issue in this case somewhat differently. aaiPharma says that the issue is whether the FDA has a duty to ensure that all eligible patents are listed in the Orange Book. In contrast, the FDA says the issue is whether it has a duty to ensure that Orange Book listings are correct (neither underinclusive nor overinclusive). For reasons that we explain below, see infra at 18-19, we do not think these different formulations of the issue have any impact on the outcome of this case because we conclude that if the FDA has a duty to police improper refusals to list patents, it must also have a duty to police improper listings of patents.

obligation to police the correctness of an NDA holder's Orange Book listings. "If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." Id. at 842-43. If, on the other hand, we find that "the statute is silent or ambiguous with respect to the specific issue, the question . . . is whether the agency's answer is based on a permissible construction of the statute." Id. at 843.

Both aaiPharma and the FDA claim that this case can be resolved at step one of the Chevron analysis because Congress has clearly expressed its intentions about the proper role of the FDA in Orange Book listing disputes. The FDA relies on the language of 21 U.S.C. § 355(c)(2), which says:

> [I]f the holder of an approved [new drug] application could not file patent information [for a patent claiming the new drug] because . . . no patent had been issued when an application was filed or approved, the holder shall file such information . . . not later than thirty days after the date the patent involved is issued. Upon the submission of patent information under this subsection, the [FDA] shall publish it.

According to the FDA, this statute clearly indicates that the NDA holder bears the sole responsibility for filing the required information on all the patents that claim its approved drug and that the FDA's role in the process is completely passive. aaiPharma relies on two different provisions, 21 U.S.C. §§ 355(d)(6) and (e)(4), to claim that Congress clearly intended for the FDA to play some role in ensuring that all eligible patents are listed in the Orange Book. Subsection (d) outlines the various grounds on which the FDA may refuse to approve an NDA. It states, among

other things, that if, after notice and an opportunity for hearing, the FDA finds that "(6) the application failed to contain the patent information prescribed by subsection (b) of this section [a list of the patents claiming the drug] . . . [it] shall issue an order refusing to approve the application." 21 U.S.C. § 355(d). Similarly, § 355(e) says that, after notice and opportunity for hearing, the FDA "shall . . . withdraw approval of an application" if it finds that "(4) the patent information prescribed by subsection (c) of this section was not filed within thirty days after the receipt of written notice from the [FDA] specifying the failure to file such information." Id. § 355(e). According to aaiPharma, these provisions indicate that the FDA has a duty to ensure that a pioneer drug company has submitted all the patents eligible for inclusion in the Orange Book.

Considered in isolation, the provisions cited by the FDA and aaiPharma could arguably qualify as clear expressions of congressional intent about the proper role of the FDA in Orange Book listing disputes. Step one of Chevron, however, requires us to look to the statute as a whole to determine whether Congress has unambiguously expressed its intent. See Mova Pharm. Corp. v. Shalala, 140 F.3d 1060, 1067-68 (D.C. Cir. 1998). Because subsection (c)(2) appears to conflict with subsections (d)(6) and (e)(4), we conclude that Congress has failed to express clearly its intent about the FDA's role in the Orange Book listing process. Accordingly, we proceed to step two of Chevron and ask whether the FDA's interpretation of its role as purely ministerial rests on a permissible construction of S 355.

There can be no question that the FDA's reading of subsection (c)(2) is reasonable. Indeed, that provision's requirement that the FDA "shall file" the patent information submitted by NDA holders is most naturally read to suggest that Congress intended for the FDA to play a purely ministerial role. The harder question is whether the

apparent reasonableness of the FDA's position is undermined by the language of subsections (d)(6) and (e)(4).

Subsection (d)(6) requires the FDA to refuse to approve an NDA that fails to contain the patent information required by § 355(b)(1), namely, a listing of the patents that claim the drug for which the application was submitted. According to aaiPharma, this provision obligates the FDA to independently determine whether the NDA applicant has listed all the patents that meet the statutory criteria for Orange Book listing. We conclude, however, that the statute can reasonably be read to impose only a much more limited duty on the FDA. This is because an NDA's "failure to contain the patent information prescribed by subsection (b)" can be understood in two different ways. On the reading proposed by aaiPharma, an NDA applicant fails to file the required patent information whenever its submissions for Orange Book listing fail to properly identify those patents that meet the statutory criteria. In other words, aaiPharma reads subsection (d)(6) to say that an NDA must be denied whenever the NDA applicant's patent law judgments are incorrect. There is, however, a far more modest interpretation of subsection (d)(6). On this more modest reading, an NDA applicant fails to file the required patent information only when it completely fails to submit a list of patents or a declaration that its drug is not claimed by any current patents. See 21 C.F.R. § 314.53(c)(3). In other words, the FDA's duty is not to ensure the correctness of the list of patents submitted for Orange Book listing, but simply to ensure that either a patent list has been filed or a declaration has been made that there are no patents to be listed. This second reading of subsection (d)(6) is at least as reasonable as the first. Further, aaiPharma's reading of subsection (d)(6) leads to an implausibly broad account of the FDA's duties under Hatch-Waxman. aaiPharma concedes that the Act does not require the FDA to assess the correctness of every determination by an NDA applicant that a patent claims or fails to claim its drug. Instead, aaiPharma contends that the

FDA must make its own determination about whether a patent is eligible for listing only if a dispute is brought to the FDA's attention. We find it difficult, however, to read subsection (d)(6) as imposing only this relatively limited enforcement obligation on the FDA. If the statute requires the FDA to police the correctness of Orange Book listings at all, the obligation is far broader than aaiPharma is prepared to acknowledge. Subsection (c)(1)(A) requires the FDA to "approve [an NDA] if [it] . . . finds that none of the grounds for denying approval specified in subsection (d) of this section applies." This means that the FDA has an obligation to evaluate every NDA for compliance with the standards in subsection (d), including the requirement in subsection (d)(6) that the application "contain the patent information prescribed in subsection (b) of this section." If as aaiPharma contends, subsection (d)(6) commands the FDA to second guess the NDA applicant's judgments about which patents claim its drug, that command is not limited to cases in which a third party has questioned the correctness of those judgments. In short, aaiPharma's reading of subsection (d)(6) must be wrong because it would require the FDA to "screen the universe of patents to determine which ones should be listed" - a result aaiPharma explicitly disclaims. Reply Brief for Appellant at 9. We conclude that on the better reading of subsection (d)(6), the FDA is required only to ensure that each NDA applicant has submitted either a list of patents claiming its drug or a declaration that there are no patents to be listed.

Section 355(e)(4) says that the FDA shall withdraw approval of an NDA if "the patent information prescribed by subsection (c) of this section [a list of patents claiming the approved drug] was not filed within thirty days after the receipt of written notice from the [FDA] specifying the failure to file such information." According to aaiPharma, this provision allows the FDA to make a written demand that an NDA holder submit a patent for listing and to enforce compliance with that demand by threatening to

withdraw approval of an NDA. The company argues that the FDA must necessarily have made a prior determination that a patent is eligible for listing before making such a written demand. This means, aaiPharma says, that the FDA has a duty to ensure that all eligible patents are listed in the Orange Book. The argument is somewhat more persuasive than aaiPharma's argument regarding subsection (d)(6). It sounds plausible to say that because subsection (e)(4) concerns the withdrawal of a previously approved NDA, its reference to an NDA holder's failure to file the patent information prescribed by subsection (c) must mean that the NDA holder has failed to list some specific patent that is eligible for listing. The conclusion appears to follow because an NDA that failed to contain a list of patents (or a declaration that there were no patents to be listed) would never have been approved in the first place. We note, however, that subsection (c)(2) requires the submission of patent information by holders of approved NDAs in two different situations. The situation emphasized by aaiPharma occurs when a new patent claiming a pioneer drug is issued after the NDA for that drug has been approved. In this situation, the NDA holder is obligated to submit the new patent for Orange Book listing no later than thirty days after the patent is issued. However, subsection (c)(2) also addresses the situation of drug companies whose NDAs were approved before the passage of the Hatch-Waxman Act. Such companies had never submitted information about patents claiming their drugs to the FDA because they were not required to do so. Subsection (c)(2) required these NDA holders to submit patents for listing in the Orange Book no later than thirty days after September 24, 1984, the date of Hatch-Waxman's enactment. We think it likely that in drafting subsection (e)(4), Congress intended to provide the FDA with a means to ensure that holders of NDAs approved prior to the Act's passage would comply with the new patent listing requirements. Accordingly, we conclude that, just as in subsection (d)(6), the "failure to file the

required patent information" discussed in subsection (e)(4) can reasonably be read to mean that the pioneer drug company has failed to submit a list of patents claiming the drug or a declaration that there are no patents to be listed. It follows that subsection (e)(4) does not undermine the reasonableness of the FDA's reading of 21 U.S.C. § 355.

Two additional points support the reasonableness of the FDA's reading of the statute. First, aaiPharma's appeals to subsections (d)(6) and (e)(4) derive much of their force from the way in which aaiPharma frames its argument. According to aaiPharma, the "failure to contain" and "failure to file" language in these subsections indicates that the FDA has a duty to intervene when pioneer drug companies fail to submit an eligible patent for listing in the Orange Book. In other words, aaiPharma explicitly claims only that the FDA has a duty to ensure that all eligible patents are listed in the Orange Book and takes no position on whether the FDA also has a duty to ensure that ineligible patents are not listed in the Orange Book. The company's argument ignores an important point. We think it clear that if Congress had intended to impose any duty on the FDA to police Orange Book listings, it would have required the FDA to ensure that ineligible patents are not listed in the Orange Book. This is because, as we noted earlier, improper listing of patents in the Orange Book is a far more serious problem than the improper refusal to list patents. By taking advantage of the thirty-month stay, a pioneer drug company that improperly lists a patent can cost consumers millions of dollars by keeping its generic competitors from bringing their products to market. In contrast, a drug company's improper refusal to list an eligible patent held by a third party like aaiPharma principally harms only the third party by depriving it of its statutory right to receive the protection of the thirty-month

stay.[7] As a result, it is hard to believe that Congress would impose a duty on the FDA to police the improper refusal to list patents without also imposing a duty to police the improper listing of patents. This means that for aaiPharma's argument to succeed, the company must show that subsections (d)(6) and (e)(4) require the FDA to ensure that Orange Book listings are correct: neither underinclusive nor overinclusive. Once this point is appreciated, aaiPharma's appeal to these subsections loses much of its force. The "failure to contain" and "failure to file" language in subsections (d)(6) and (e)(4) makes sense if, as we suggest, these provisions simply require the FDA to ensure that patent lists are submitted in a timely fashion. It might also make sense if Congress had intended to require the FDA to police only improper refusals to list patents in the Orange Book. But it seems odd language in which to articulate a general FDA duty to ensure that Orange Book listings are correct. We conclude that if Congress had meant for the FDA to ensure that Orange Book listings are neither underinclusive nor overinclusive, it would have not have used the language it did in subsections (d)(6) and (e)(4).

Second, the FDA's reading of the statute is reasonable in light of the division of intellectual labor established by the Hatch-Waxman Act. The FDA points out that the whole point of the Act's paragraph IV certification scheme is to let private parties sort out their respective intellectual property rights through patent infringement suits while the FDA focuses on its primary task of ensuring that drugs are safe and effective. This division of labor is appropriate because the FDA has no expertise in making patent law judgments. It seems unlikely, then, that Congress intended to require the FDA to take on the responsibilities

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[7] It is important to recognize that the third-party patentee can still pursue patent infringement suits against generic manufacturers. It is simply deprived of the opportunity to litigate its infringement claims under the shelter of the thirty-month stay.

urged upon it by aaiPharma. For all these reasons, we conclude that the FDA's conception of its role in Orange Book listings as purely ministerial rests on a permissible construction of § 355.

aaiPharma also contends that the FDA's refusal to police the correctness of Orange Book listings is arbitrary and capricious in violation of the APA because it delegates the FDA's statutory responsibilities to private parties. aaiPharma claims that it is arbitrary for the FDA to allow NDA holders, in their unreviewable discretion, to determine whether eligible patents are listed in the Orange Book. According to aaiPharma, the inevitable result of the FDA's policy is that similarly situated patent holders will be treated differently. We are unpersuaded. The first problem with the argument is that by accusing the FDA of wrongfully delegating its statutory duties to NDA holders, aaiPharma assumes that the FFDCA imposes these statutory duties on the FDA in the first place. This, of course, is the very question at issue. As we have already explained, the FDA's conclusion that it has no statutory duty to police the correctness of Orange Book listings rests on a permissible construction of the statute. Further, we think that the FDA has provided a reasoned explanation for its policy that is sufficient to satisfy the standard of review set forth in Motor Vehicle Mfrs. Ass'n of the United States, Inc. v. State Farm Mutual Auto. Ins. Co., 463 U.S. 29, 43 (1983). In State Farm the Supreme Court explained that the scope of review under the arbitrary and capricious standard is narrow. We must ensure that "the agency [has] examine[d] the relevant data and articulate[d] a satisfactory explanation for its action including a rational connection between the facts found and the choice made." Id. (internal quotation marks and citation omitted). An agency rule would normally be arbitrary and capricious, however, if "the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to

the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise." Id. In issuing its final rules regarding the patent listing requirements imposed by Hatch-Waxman, the FDA explicitly considered objections to its proposed § 314.53(f). Two commenters argued that the FDA should "ensure that the patent information submitted to the agency is complete and applies to a particular NDA." Abbreviated New Drug Application Regulations, Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,345 (Oct. 3, 1994). The FDA responded that it did not have "the resources or the expertise to review patent information for its accuracy and relevance to an NDA." Id. It also pointed out that an NDA applicant's potential liability for submitting untrue statements of fact to the agency would provide some check against abuse of the listing process. Finally, the agency observed that the informal procedure described in § 314.53(f) had proven effective in the past because "most NDA holders have amended or corrected their patent information after FDA has informed them of a dispute." Id. These explanations of the FDA's position are not especially detailed, but we cannot say the agency's decision making was arbitrary and capricious. As we have explained, the FDA was asked by commenters to take on enforcement responsibilities that are not clearly imposed by its governing statute. When an agency has discretion about whether to take on enforcement responsibilities, an explanation that it lacks the resources and the expertise to do so is enough to satisfy the requirement of reasoned agency decision making articulated in State Farm.

None of this is to say that we are unsympathetic to aaiPharma's concerns. We agree with aaiPharma that Hatch-Waxman protects the intellectual property rights of third-party patentees and that, if the '853 patent claims Prozac, aaiPharma is entitled to enjoy the benefits of the thirty-month stay. Ultimately, aaiPharma's argument boils down to the plausible claim that if NDA holders have a statutory

obligation to submit the correct list of patents for publication in the Orange Book and the failure to comply with that obligation deprives third parties of benefits conferred by Congress, there must be some mechanism to enforce this obligation. Because the FFDCA clearly does not allow private enforcement of an NDA holder's listing obligations, aaiPharma concludes that enforcement responsibility must fall on the FDA and that the agency's refusal to accept that responsibility is arbitrary and capricious. Although we find some force in this argument, we cannot accept the proposition that an agency's failure to fill an enforcement gap created by a statute is necessarily

arbitrary and capricious.[8] We conclude that until Congress takes further action to address the enforcement gap in Hatch-Waxman's patent listing provisions, the FDA may persist in its purely ministerial approach to the Orange Book listing process.

V.

For the foregoing reasons, the district court's order rejecting aaiPharma's APA challenge is affirmed.

AFFIRMED

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[8] We are encouraged to learn that there does appear to be at least one mechanism for enforcing an NDA holder's obligation not to list patents that do not claim its approved drug. Generic drug manufacturers, state agencies, and consumer groups have begun to bring antitrust suits against NDA holders who seek to use improper Orange Book listings to extend their monopoly power. See In re Buspirone Patent Litigation, 185 F. Supp. 2d 363 (S.D.N.Y. 2002). The Federal Trade Commission has also begun to address the potentially anticompetitive effects of improper Orange Book listings. See Prepared Statement of the Federal Trade Commission Before the Committee on Commerce, Science, and Transportation, United States Senate (April 23, 2002), available at www.ftc.gov/os/2002/04/pharmtestimony.htm.

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NORTH CAROLINA
SOUTHERN DIVISION
No. 7:01-CV-152-F1

aaiPHARMA, INC., Plaintiff, v. TOMMY G. THOMPSON, Secretary of Health and Human Services, BERNARD SCHWETZ, DVM, Ph.D., Acting Commissioner of United States Food and Drug Administration; and UNITED STATES FOOD and DRUG ADMINISTRATION, Defendants.	)	ORDER

Filed: August 13, 2001

This matter came on for hearing before the undersigned on August 2, 2001, upon the plaintiff's Motion for Preliminary Relief filed that same day. Specifically, the plaintiff, aaiPharma, Inc. (hereinafter "aai") sought an injunction, the effect of which would be to block final FDA approval of generic equivalents of the widely-prescribed antidepressant drug, Prozac®, the patent for which was to expire at 11:59 p.m. on August 2, 2001.

aai is a Delaware corporation with its principal place of business in Wilmington, North Carolina. The defendants are federal entities - specifically, the Secretary of Health and Human Services, the Acting Commissioner of the Food and Drug Administration (hereinafter "FDA"), and the FDA itself.

Physically present at the hearing were Messrs. Richard P. Vitek and Alan E. Toll on behalf of the plaintiff, aai, and Assistant United States Attorney Norman Acker representing the defendants. Ms. Barbara Stradling of the United States Department of Justice, and Mr. Mike Druckman of the Food and Drug Administration were present by telephone from Washington, D.C. At the outset of the hearing, the undersigned informed all present that he and a family trust hold substantial shares in certain drug companies, including Merck, Lilly, Johnson & Johnson, Bristol-Myers Squibb, Abbott Labs, American Homes and Glaxco, as disclosed in his financial disclosure statement on file with the Administrative Office of the United States Courts. Although the undersigned offered to recuse if any party was at all uncomfortable with his hearing the matter, counsel for both sides assured the court that there were no objections.

STATUTORY/REGULATORY SCHEME[1]

A company wishing to market a new drug must seek the approval of the FDA by completing a "New Drug Application" (hereinafter "NDA"). *See American Bioscience, Inc. v. Thompson*, 243 F.3d 579, 580 (D.C. Cir. 2001). An NDA is costly and time-consuming to prepare because it must include data from studies showing the drug's safety and effectiveness. *See Mova Pharmaceutical Corp. v Shalala*, 140 F.3d 1060, 1063 (D.C. Cir. 1998). Before 1984, a company seeking to make a generic version of an FDA-approved brand-name drug ("generic maker") was required to file

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[1] Much of the following section is shamelessly derived from Judge Urbina's excellent overview in *MyLan PharmaceuticaLs, Inc, v, Thompson*, 139 F. Supp. 2d 1, *4-*7 (D.D.C. 2001) of the Hatch-Waxman Act framework, which in turn was heavily relied upon in *Andrx Pharmaceuticals, Inc. v. Biovail Corp Int'l*, Nos. 00-5050 & 00-5396, 2001 WL 855472 (D.C. Cir. July 31, 2001).

another NDA and conduct another costly and timeconsuming study. In 1984, Congress enacted the Hatch-Waxman Amendments to the Food, Drug and Cosmetic Act ("FDCA") to simplify the procedure for FDA approval. *See* Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified at 21 U.S.C. § 355 and 25 U.S.C. §§ 156 and 271(e)).

Under the Hatch-Waxman Act, the original applicant for FDA approval (the "pioneer" applicant) still must prepare an NDA. Subsequent applicants who wish to manufacture generic[2] versions of the pioneer drug, however, need only complete an Abbreviated New Drug Application (hereinafter "ANDA") that relies on the FDA's previous determination that the drug is safe and effective. *See Mova*, 140 F.3d at 1063.

Although Congress was interested in increasing the availability of generic drugs, it also wanted to protect the patent rights of the pioneer applicants. *See* David A. Balto, *Pharmaceutical Patent Settlements: The Antitrust Risks*, 55 FOOD & DRUG L.J., 321, 324 (2000) (hereinafter "Balto"). Therefore, the 1984 amendments require that an NDA contain a list of any patents "which claim[] the drug ... or which claim[] a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." 21 U.S.C. § 355(b)(1). If such a patent is issued after the pioneer-maker's NDA is approved, as here, the statute provides that:

> if the holder of an approved application could not file patent information under

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[2] "Generic" drugs are versions of brand-name prescription drugs that typically contain the same active ingredients but not necessarily the same inactive ingredients as the brand-name original. *See United States v. Genrix Drug Corp.*, 460 U.S. 453, 454-55 (1983)..

> subsection (b) because no patent had been issued when an application was fled or approved, the holder shall file such information under this subsection not later than thirty days after the date the patent involved is issued. Upon the submission of patent information under this subsection, the Secretary shall publish it.

Id. at § 355 (c)(2). The FDA maintains a record of all such information in its publication commonly known as the Orange Book. *See* 21 U.S.C. § 355(j)(7)(A).

aai owns patent '853 that purportedly describes and claims the "Form A" component of fluoxetine hydrochloride, the active ingredient in Lilly's Prozac®. aai is not now prepared to test, manufacture, advertise, distribute and sell a generic consumer drug containing its patented chemical compound, and it does not seek either an NDA or an ANDA. Rather, it seeks to stake out its claim to the entire generic Prozac® market until it is ready to do so, and, in the meantime, to prevent current interim ANDA-holders and other generic drug manufacturers from obtaining final FDA approval for their generic Prozac® equivalents. That is, aai seeks to compel compliance with § 355(c)(2) which aai contends requires that its '853 patent must be listed in the Orange Book as "claiming" Form A of the active ingredient in Prozac® or a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted.

If the '853 patent were identified and listed in the Orange Book before the Prozac patent expired at 11:59 p.m. on August 2, 2001, then the several generic drug manufacturers that now are poised to place their products on the market at midnight would be stopped dead in their tracks by § 355(j)(2)(A)(vii). That provision requires that an

ANDA applicant make one of four certification options to the FDA.[3]

In this case, if aai were to obtain a mandatory injunction requiring the FDA to list its '853 patent in the Orange Book before midnight on August 2, then the ANDA applicants would have had to choose ¶ IV, certifying that "the patent is invalid or will not be infringed by the drug for which the applicant seeks approval." § 355(j)(2)(A)(vii).

> A Paragraph [iv] certification has significant legal effects. . . . The patent law provides that submitting an application for an infringing product is itself an act of infringement.... Thus, a Paragraph IV certification automatically creates a cause of action for patent infringement. . . . Upon receiving notice of -a Paragraph IV certification, the patent holder has 45 days in which to file suit against the generic manufacturer. See 21 U.S.C. § 355(j)(5)(B)(iii). If the patent-holder brings such an action, the FDA is prohibited from approving the generic maker's ANDA for a period of 30 months. . . . This 30-month stay allows the parties to litigate the patent infringement action in court. . . .

Mylan Pharmaceuticals, 139 F. Supp. at *6-*7 (footnotes and citations omitted).

Therefore, aai is not attempting by this lawsuit to place a generic equivalent of Prozac® on the market.

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[3] It may certify that (I) the required patent information has not been filed, (II) the patent has expired, (III) the patent has not expired but will expire on a particular date, or (IV) the patent is invalid or will not be infringed by the drug for which the applicant seeks approval. *See* 21 U.S.C. § 355(j)(2)(A)(vii) .

Rather, aai is attempting to prevent any other drug maker from doing so until aai can litigate patent infringement claims against those generic drug makers and ANDA applicants who are now ready to place their generic equivalents of Prozac® into the stream of commerce.

FINDINGS OF FACT

As it did not appear that there were material issues of fact for purposes of the hearing on the temporary restraining order, the court draws the following findings of fact from aai's Verified Complaint and Memorandum for Preliminary Relief.

1. On July 10, 2001, United States Patent No. 6,258, 853 ("the'853 patent") was issued to aai by the United States Patent Office.

2. aai alleges that its '853 patent describes and claims pharmaceutical formulations comprising the Form A component of fluoxetine hydrochloride at specified purity levels, and methods of using these formulations. Fluoxetine hydrochloride, a member of the class of antidepressants known as Selective Serotonin Reuptake Inhibitors, is the active pharmaceutical ingredient in Lilly's Prozac®. Form A of fluoxetine hydrochloride is a polymorphic variant, or component, of fluoxetine hydrochloride. aai's counsel described it at the hearing as an "improvement on Prozac®."

3. aai requested that Lilly amend its NDA for Prozac® to identify the '853 patent to the FDA for listing in the Orange Book, but Lilly declined to do so.

4. On July 18, 2001, aai sent a letter to the FDA requesting that it vindicate aai's patent rights under the Hatch-Waxman Act. The FDA's response was to send a letter to Lilly, the NDA holder, advising Lilly of aai's concerns and confirming that the FDA would not list aai's patent unless Lilly identified it in its NDA for Prozac®.

5. Lilly's claim for Prozac's® exclusivity under the patent laws was scheduled to expire at or about 11:59 p.m. on August 2, 2001.

6. Several companies had submitted ANDAs for generic versions of Prozac®. However, because Lilly did not identify aai's '853 patent under its Prozac® NDA, the '853 patent was not published in the Orange Book, and those generic companies were not required to submit ¶ IV certifications claiming invalidity or non-infringement of the '853 patent.

7. Unless injunctive relief were ordered, the FDA's tentative approval of the ANDAs for the generic versions of Prozac® would become effective at midnight on August 2/3, 2001, and aai's window of opportunity to litigate its '853 patent claims without competition from the generic makers it is suing would slam shut.

ANALYSIS

aai's Verified Complaint, filed August 2, 2001 - the day on which Lilly's patent was to expire - seeks (i) a temporary restraining order and a preliminary injunction enjoining the defendants from issuing final approval of any ANDA for a generic version of Prozac® pending a determination whether the '853 patent is required to be identified in Lilly's NDA for Prozac® and listed in the Orange Book; and (ii) an order requiring the defendants to (a) take all necessary steps to require Lilly to amend its NDA to identify the '853 patent and its expiration date, and upon such identification, (b) publish the information in the Orange Book. aai's relief, if any, must have been had before midnight on August 2, 2001, or its claim would be moot. In seeking such relief, it is aai's position that Congress entrusted the FDA with a non-delegable duty to take affirmative independent action upon notification from a third party (here, aai) that a patent qualifying for Orange

Book listing has been issued, and then to cause such patent information to be published in the Orange Book.

Because the FDCA does not provide a private right of action, see, e.g., *Mylan Labs, Inc, v. Matkari*, 7 F.3d 1130, 1139 (4th Cir. 1993), *cert. denied*, 510 U.S. 1197 (1994), aai has sued the FDA under the Administrative Procedures Act ("APA"), 5 U.S.C. §§ 701 et seq., alleging that the FDA impermissibly delegated its responsibility to Lilly, a private, commercial drug manufacturer "necessarily motivated by pure self-interest" to identify and list qualifying patents (such as aai's own '853) in the Orange Book. aai's Memorandum in Support of Preliminary Relief at 14. aai alleges that the FDA's delegation of its power is "arbitrary, capricious, an abuse of discretion, [and] otherwise not in accordance with law." aai contends that "[i]f the Court does not enjoin the Secretary, the Acting Commissioner, and the FDA, aaiPharma effectively will be deprived of its statutory rights under the Hatch-Waxman Act." aai's Memorandum at 15.

The APA provides for judicial review of adverse federal agency actions. Here, the alleged adverse agency action is the FDA's refusal to act in accordance with aai's request, but allegedly consistent with the requirements of the controlling statute and FDA regulations promulgated thereunder. Although aai argues that it seeks injunctive relief to preserve the status quo pending a more leisurely inquiry on the merits, in fact aai seeks an order from this court directing the FDA to take affirmative action inconsistent with its own regulations, the result of which actually will upset the status quo. The status quo as of the date and time aai filed its Verified Complaint was that the '853 patent was not listed in the Orange Book, Lilly's period of exclusivity for its Prozac® NDA was to expire in about twelve hours, and a number of other generic manufacturers holding tentatively approved ANDAs awaiting final

approval upon expiration of the Prozac® patent were poised to place their products on the market.[4]

Courts in the Fourth Circuit have been directed to apply a balancing-of-the hardships test when considering a motion for preliminary injunctive relief. *See Blackwelder Furniture Co. of Statesville, Inc. v. Seilig Mfg. Co., Inc.*, 550 F.2d 189, 195 (4th Cir. 1997). The now-familiar "*Blackwelder* balancing test" recently has been explained as follows:

> A court must consider (1) the likelihood of irreparable harm to the plaintiff if the preliminary injunction is denied; (2) the likelihood of harm to the defendant if the request is granted; (3) the likelihood that the plaintiff will succeed on the merits; and (4) the public interest.
>
> "[T]he first step ... is for the court to balance the 'likelihood' of irreparable harm to the plaintiff against the 'likelihood' of harm to the defendant; and if a *decided* imbalance of hardship should appear in plaintiff's favor, then ... [i]t will ordinarily be enough that the plaintiff has raised questions going to the merits so serious, substantial, difficult, and doubtful, as to make them fair ground for litigation. . . . "But "if 'the plight of the defendant [is] not substantially different from that of the plaintiffs,' that is, if there is no imbalance of hardship in favor of the plaintiff, then 'the probability of success begins to assume real significance,' and

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[4] Counsel for the defendants advised during the hearing that he understood the ANDAs already had received final approval because the FDA was required by law to act on those applications that day. *See* Hearing Transcript at 31.

> interim relief is more likely to require a clear showing of a likelihood of success."

Microstrategy, Inc. v. Motorola, Inc., 345 F.3d 335, 339 (4th Cir. 2001) (citations omitted).

The Fourth Circuit Court of Appeals went on to comment in *Microstrategy* that when the balance of hardships does not tilt decidedly in favor of the plaintiff, then the plaintiff must make a "'strong showing of likelihood of success' or a 'substantial likelihood of success' by 'clear and convincing evidence.'" *Id.* at 340 (quoting *Direx Israel, Ltd v. Breakthrough Medical Corp.*, 952 F.2d 802, 818 (4th Cir. 1991)) (internal quotation marks and citations omitted in original). Moreover,

> [a]s we noted in *Direx*, the foremost trademark authority has stated that "when the hardship balance does not tip 'decidedly' or 'significantly' in favor of the plaintiff," then the plaintiff must prove the "'probability (not mere possibility)' " of success on the merits; in other words, the plaintiff must have "a very clear and strong case." *Direx*, 952 F.2d at 813 (quoting 2 J. THOMAS MCCARTHY ON TRADEMARKS AND UNFAIR COMPETITION § 30.16 (2d ed. 1980)). "'To doubt is to deny"; thus, "if there is doubt as to the probability of plaintiff's ultimate success on the merits, the preliminary injunction must be denied." *Id.*

Microstrategy, 245 F.3d at 340. With these directives in mind, the court applies the *Blackwelder* factors to the facts presented in this case.

I. Likelihood of Irreparable Harm to the Plaintiff

aai contends that absent a restraining order "preserving the status quo," it will immediately and permanently lose "its critical statutory rights under the Hatch-Waxman Act." aai's Memorandum at 15. However, aai neglects to identify exactly what critical statutory rights it is in danger of permanently losing so as to justify imposition of the emergency injunctive relief it seeks. While aai argues that the Hatch-Waxman Act was enacted in order to protect pioneer drug patent-holders and to encourage innovation by generic drug manufacturers, aai itself falls into neither of these categories. aai holds an independent patent but, rather than undergo the lengthy and expensive NDA process, it seeks recognition of its patent under Lilly's NDA. And by obtaining such recognition, aai effectively would block distribution of all other generic Prozac® equivalents while it prosecutes patent infringement actions against holders of ANDAs. In short, aai seeks to foreclose competition for more than two years as it enjoys more protection for its patent than Lilly had in developing its pioneer drug, Prozac®. The court does not perceive that this is what Congress had in mind at all in enacting the Hatch-Waxman Act.

aai holds a patent, and by virtue thereof, owns the right to sue for damages, injunctive relief and attorney's fees under federal patent law. Indeed, aai already has sued five generic drug manufacturers for alleged infringement of the '853 patent. *See aaiPharma, Inc, v. Barr Laboratories, Inc., et al.* No. 7:01-CV-150-F1 (E.D.N.C.) (filed August 1, 2001). That aai is not entitled to enjoy the unfettered thirty-month period it seeks within which to prevent other generic drug manufacturers from marketing their products does not constitute irreparable harm; aai may be made whole by money damages if it prevails on its patent infringement claims against those entities.

II. Likelihood of Harm to the Defendant

Here, the "likelihood of harm to the defendant" prong of the *Blackwelder* test is not technically pertinent; the defendants are Governmental entities. Rather, the harm from allowing the injunctive relief aai seeks would be suffered by the generic drug manufacturers who hold conditionally approved ANDAs and by the consuming public. Through the Hatch-Waxman Amendments, "Congress sought to get generic drugs into the hands of patients at reasonable prices - fast." *In re Barr Laboratories, Inc.*, 930 F.2d 72, 76 (D.C. Cir.), cent, denied, 502 U.S. 906 (1991). Granting aai an injunction would be inconsistent with this objective. The potential losses to the generic drug manufacturers include loss of product due to expiration of shelf life, manufacturing costs, and loss of profits, as well as incentive.

III. Likelihood of Success on the Merits

Because the balance of hardship does not "tilt decidedly in plaintiffs favor," *Direx*, 952 F.2d at 818, then it is up to aai, now, to prove the probability - not just a possibility - that it will succeed on the merits of its claim that the FDA has improperly delegated its authority to enforce the FDCA to Lilly in violation of the APA.

At the heart of this lawsuit is aai's allegation that its '853 patent must be identified as claiming "pharmaceutical formulations comprising the Form A component of" the active ingredient in Lilly's Prozac®, and that such patent information be published in the Orange Book. The gravamen of aai's Verified Complaint is that it is the FDA's responsibility both to identify the patent - and/or see that it is identified - and then to publish notice of it.

aai explains that, pursuant to 21C.F.R. § 314.53(f), it notified Lilly of the '853 patent and requested that Lilly amend its NDA to identify the '853 patent. Lilly, however,

declined to amend its NDA or otherwise notify the FDA. Therefore, on July 18, 2001, aai wrote a letter to the FDA requesting that it "vindicate" aai's patent rights, but the FDA's response merely was to forward aai's request to Lilly, and to advise aai that the FDA would not list the '853 patent in the Orange Book unless Lilly identified it in its Prozac® NDA.

As enacted by Congress, the governing statute reads:

> [I]f the holder of an approved application could not file patent information under [21 U.S.C: § 355(b)] because no patent had been issued when an application was filed or approved, the holder shall file such information under this subsection not later than thirty days after the date the patent is issued. **Upon the submission of patent information under this subsection, the Secretary [of the FDA] shall publish it [in the Orange Book].**

21 U.S.C. § 355(c)(2) (emphasis added).

Regulations published by the FDA for use in this situation provide in pertinent part:

> (f) Correction of patent information errors. If any person ... believes that an applicant has failed to submit required patent information, that person must first notify the agency in writing stating the grounds for disagreement.... The agency will then request of the applicable new drug application holder that the correctness of the patent information or omission of patent information be confirmed. **Unless the application holder withdraws or amends its patent information in response to FDA's request, the agency**

> **will not change the patent information in the list.** If the new drug application holder does not change the patent information submitted to FDA, . . . an [ANDA] under section 505(j) of the act submitted for a drug that is claimed by a patent for which information has been submitted must, despite any disagreements as to the correctness of the patent information, contain an appropriate certification for each listed patent.

21 C.F.R. § 314.53 (emphasis added).

aai acknowledges that the FDA's regulations and practices expressly decline to authorize the FDA to become involved in Orange Book disputes. *E.g.*, 21 C.F.R. § 314.43; *Mylan Labs v Thompson*, 139 F. Supp. 2d at *10-11 ("Noting that the FDA plays a limited, 'ministerial' role in the patent fights between patent holders and generic makers, and in light of the traditional deference accorded to agency determinations, Judge Smalkin ruled that it was 'not the business of the FDA or of this Court in an APA review, to adjudicate the *merits* of the scope and/or validity of the claims covered by the . . . patent'") (quoting *Watson Pharm., Inc. v. Henney*, Civil Action No. 00-3516 (D. Md. Jan. 17, 2001)) (emphasis in original). However, by taking such a position, aai argues, the FDA's conduct is arbitrary and capricious and thus impermissible under the APA.

A court's inquiry into agency action under the APA is highly deferential. An agency's action may be set aside only if it is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(a)(2). "In exercising its narrowly defined duty under the APA, the court must consider whether the agency acted within the scope of its legal authority, adequately explained its decision, based its decision on facts in the record, and

considered the relevant factors." *National Park and Conservation Ass'n v. Stanton*, 54 F. Supp. 2d 7, 11 (D.C. Cir. 1999) (citing *Marsh v. Oregon Natural Resources Council*, 490 U. S. 360, 378 (1989); *Citizens to Preserve Overton Park, Inc. v, Volpe*, 401 U.S. 402, 415-16 (1971)).

Notwithstanding aai's argument to the contrary, Congress did not direct the FDA to undertake to identify patents that qualify for Orange Book listing. And aai misses the point when it contends that "the FDA's regulations and practices under which it expressly declines to become involved in Orange Book disputes ... delegate[] unreviewable discretion to the NDA holder to determine whether the standards for identifying and thus effectively for [sic] listing patents under the Hatch-Waxman Act have been met constitute a clear violation of the APA." aai's Memorandum at 13 (footnote omitted). The FDA's refusal to act on aai's demand to list the `853 patent was not predicated just on its "regulations and practices;" the FDA regulations and practices themselves derive from Congress's directive that:

> [I]f the holder of an approved application could not file patent information under [21 U.S.C. § 355(b)] because no patent had been issued when an application was filed or approved, the holder shall file such information under this subsection not later than thirty days after the date the patent is issued. **Upon the submission of patent information under this subsection, the Secretary [of the FDA] shall publish it [in the Orange Book]**.

21 U.S.C. § 355(c)(2) (emphasis added). Congress does not delegate to the FDA the task of identifying patents for listing in the Orange Book; Congress requires that *upon submission of patent information,* the FDA *shall publish it* in the Orange

Book. *See id.* The onus is placed on an NDA-holder to identify qualifying patents and then to provide the required information to the FDA. If the NDA holder does not so do, the regulations provide that a third party may bring such failure to the FDA's attention. *See* 21 C.F.R. § 314.53(f). In no event, however, is the FDA required by statute, regulation or practice to undertake, sua sponte, the Orange Book listing of a patent. So far as this court can determine, a party in aai's situation has no redress if the NDA-holder elects not to notify the FDA of a qualifying patent. Therefore, the very premise upon which aai's lawsuit is based simply is not correct.

aai has offered no authority for its assertion that the FDA has delegated authority conferred upon it by Congress by its declining to undertake to identify patents that qualify for Orange Book listing, and the court has been unable to locate any such authority. In fact, the allegations in the Verified Complaint carefully omit reference to the terms of the statute and, rather, refer only to the "regulations and practices" of the FDA. *See, e.g.*, Verified Complaint ¶ 10 ("However, under its regulations and practice, the FDA will not undertake an independent evaluation of the non-NDA holder's claim that its patent should be listed, and will not either require the NDA holder to identify a patent for listing or publish the patent information in the Orange Book"). Congress decided that the FDA's task simply is to publish - without question - whatever patent information , if any, as is supplied to it by the NDA holder pursuant to the statute.

IV. The Public Interest

Although the court concludes that aai has little or no chance of prevailing on a substantive claim that the FDA is impermissibly delegating its authority to private drug companies, the court nevertheless finds it appropriate to comment on the final *Blackwelder* factor, the interest of the public. aai did not address the public interest in its

Memorandum or during its presentation at oral argument of the instant motion. The court does not have before it statistics purporting to demonstrate the cost and availability of widely-prescribed brand-name drugs such as Prozac® or the effect upon the general public's ability to obtain the benefit of the a generic version that the FDA's approval of generic equivalents would have. While the court recognizes the strong public interest in encouraging drug manufacturers to engage in research and development of new and better drugs, aai has failed to demonstrate how allowing its motion for injunctive relief would advance that interest. As noted above, the Hatch-Waxman Act was not designed to protect a company in aai's shoes. The public interest in lower-priced, hence, more available, prescription drugs far outweighs aai's interest in preventing competition and generating staggering profits while it litigates its patent claims against the generic manufacturers. That the Hatch - Waxman Amendments are subject to manipulation to competitive advantage has not been lost on the commentators and to other courts. *Cf. Andrx Pharmaceuticals*, 2001 WL 855472 at *11 ("'The competitive concern is that the 180-day exclusivity provision can be used strategically by a patent holder to prolong its market power in ways that go beyond the intent of the patent laws and the Hatch-Waxman Act by delaying generic entry for a substantial period.'") (quoting Balto, *supra*, at 331). Although there certainly is no suggestion here that aai was in collusion with Lilly or anyone else, the net result is the same, and that result simply is not consistent with the stated objectives of the Hatch Waxman Act or the public interest.

Based on the foregoing FINDINGS OF FACT and analysis, the court hereby enters the following:

CONCLUSIONS OF LAW

1. This court has jurisdiction over this action under 28 U.S.C. § 1331 and 5 U.S.C. § 703.

2. Venue is proper in this district pursuant to 28 U.S.C. § 1391 and 21 U.S.C. § 355(c)(3).

3. Because aai has an adequate remedy at law through prosecution of its patent infringement claims against alleged infringers of its '853 patent, aai will not suffer irreparable harm if the court denies the injunctive relief it seeks. The balance of harms does not favor aai but, rather, tips decidedly in favor of protection of the generic drug manufacturers and the general public.

4. Because the FDA is not required by statute to investigate and identify patents that must be listed in the Orange Book, aai is unlikely to prevail on the merits of its claim that the FDA has violated the Administrative Procedures Act by delegating to Lilly the task of identify aai's '853 patent for publication in the Orange Book.

5. The public interest in the availability of lower-priced generic equivalent drugs strongly favors denial of aai's motion for injunctive relief.

For these reasons, therefore, and based on the foregoing FINDINGS OF FACT and CONCLUSIONS OF LAW, it hereby is ORDERED that aai's Motion for Preliminary Relief is DENIED. Because this order effectively is a ruling against aai "on the merits," the Clerk of Court is DIRECTED to enter judgment and to close this file.

SO ORDERED.

This 10th day of August, 2001.

/s/
JAMES C. FOX
Senior United States District Judge

United States District Court
EASTERN DISTRICT OF NORTH CAROLINA

aaiPHARMA, INC., Plaintiff,	)
v.	)
TOMMY G. THOMPSON, Secretary of Health and Human Services, BERNARD SCHWETZ, DVM, Ph.D. Acting Commissioner of United States Food and Drug Administration; and UNITED STATES FOOD and DRUG ADMINISTRATION, Defendants.	)

JUDGMENT IN A CIVIL CASE
NO. 7:01-CV-152-F(1)

Filed: August 13, 2001

____ **Jury Verdict**. This action came before the Court for a trial by jury. The issues have been tried and the jury has rendered its verdict.

_X_ **Decision by Court**. This action came to trial or hearing before the Court. The issues have been tried or heard and a decision has been rendered.

IT IS ORDERED AND ADJUDGED that aai's Motion for Preliminary Relief is DENIED. Because the order of August 10, 2001 is a ruling against aai "on the merits," the Clerk of Court is DIRECTED to enter judgment and to close this file.

THE ABOVE JUDGMENT WAS ENTERED TODAY, **August 13, 2001** AND A COPY MAILED TO:

Alan E. Tool, Esq.
Stevens, McGhee, Morgan,
Lennon & O'Quinn
P.O. Drawer 59
Wilmington, NC 28402

G. Norman Acker III, Esq.
U.S. Attorney's Office
310 New Bern Ave.
Suite 800
Raleigh, NC 27601

August 13, 2001
Date

DAVID W. DANIEL,
Clerk *Eastern District of North Carolina*

Wilmington, North Carolina

/s/ illegible
(By) Deputy Clerk

UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT
FILED
September 9, 2002

AAIPHARMA INCORPORATED,
Plaintiff - Appellant,

v.

No. 01-2113
CA-01-152-F

TOMMY G. THOMPSON, Secretary of Health and Human Services; BERNARD SCHWETZ, DVM, Ph.D., Acting Commissioner of United States Food and Drug Administration; UNITED STATES FOOD AND DRUG ADMINISTRATION,
Defendants - Appellees,

BARR LABORATORIES, INCORPORATED; PHARMACEUTICAL, INCORPORATED,
Intervenors.

ON PETITION FOR REHEARING AND REHEARING EN BANC

The appellant's petition for rehearing and rehearing en banc was submitted to this Court. As no member of this Court or the panel requested a poll on the petition for rehearing en banc, and

As the panel considered the petition for rehearing and is of the opinion that it should be denied,

IT IS ORDERED that the petition for rehearing and rehearing en banc is denied.

For the Court,

/s/ Patricia S. Connor
Clerk

21 U.S.C. § 355(a) – (i) - New drugs

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.

(b) Filing application; contents

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application

(A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use;

(B) a full list of the articles used as components of such drug;

(C) a full statement of the composition of such drug;

(D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug;

(E) such samples of such drug and of the articles used as components thereof as the Secretary may require; and

(F) specimens of the labeling proposed to be used for such drug. The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences. The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by clause (A).

(2) An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted shall also include -

(A) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under paragraph (1) or subsection (c) of this section -

(i) that such patent information has not been filed,

(ii) that such patent has expired,

(iii) of the date on which such patent will expire, or

(iv) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(B) if with respect to the drug for which investigations described in paragraph (1)(A) were conducted information was filed under paragraph (1) or subsection (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

(3)

(A) An applicant who makes a certification described in paragraph (2)(A)(iv) shall include in the application a statement that the applicant will give the notice required by subparagraph (B) to -

(i) each owner of the patent which is the subject of the certification or the representative of such owner designated to receive such notice, and

(ii) the holder of the approved application under subsection (b) of this section for the drug which is claimed by the patent or a use of which is claimed by the patent or the representative of such holder designated to receive such notice.

(B) The notice referred to in subparagraph (A) shall state that an application has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification. Such notice shall include a detailed statement of the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed.

(C) If an application is amended to include a certification described in paragraph (2)(A)(iv), the notice required by subparagraph (B) shall be given when the amended application is submitted.

(4)

(A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1) or under section 262 of title 42, which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.

(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection or section 262 of title 42 if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an effectiveness claim. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of the clinical trials. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant upon request.

(C) Any agreement regarding the parameters of the design and size of clinical trials of a new drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except -

(i) with the written agreement of the sponsor or applicant; or

(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance division personnel unless such field or compliance division personnel demonstrate to the reviewing division why such decision should be modified.

(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.

(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection or section 262 of title 42 (including all scientific and medical matters, chemistry, manufacturing, and controls).

(c) Period for approval of application; period for, notice, and expedition of hearing; period for issuance of order

(1) Within one hundred and eighty days after the filing of an application under subsection (b) of this section, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either -

(A) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) of this section applies, or

(B) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) of this section on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an

expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(2) If the patent information described in subsection (b) of this section could not be filed with the submission of an application under subsection (b) of this section because the application was filed before the patent information was required under subsection (b) of this section or a patent was issued after the application was approved under such subsection, the holder of an approved application shall file with the Secretary the patent number and the expiration date of any patent which claims the drug for which the application was submitted or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If the holder of an approved application could not file patent information under subsection (b) of this section because it was not required at the time the application was approved, the holder shall file such information under this subsection not later than thirty days after September 24, 1984, and if the holder of an approved application could not file patent information under subsection (b) of this section because no patent had been issued when an application was filed or approved, the holder shall file such information under this subsection not later than thirty days after the date the patent involved is issued. Upon

the submission of patent information under this subsection, the Secretary shall publish it.

(3) The approval of an application filed under subsection (b) of this section which contains a certification required by paragraph (2) of such subsection shall be made effective on the last applicable date determined under the following:

(A) If the applicant only made a certification described in clause (i) or (ii) of subsection (b)(2)(A) of this section or in both such clauses, the approval may be made effective immediately.

(B) If the applicant made a certification described in clause (iii) of subsection (b)(2)(A) of this section, the approval may be made effective on the date certified under clause (iii).

(C) If the applicant made a certification described in clause (iv) of subsection (b)(2)(A) of this section, the approval shall be made effective immediately unless an action is brought for infringement of a patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (3)(B) is received. If such an action is brought before the expiration of such days, the approval may be made effective upon the expiration of the thirty-month period

beginning on the date of the receipt of the notice provided under paragraph (3)(B) or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that -

(i) if before the expiration of such period the court decides that such patent is invalid or not infringed, the approval may be made effective on the date of the court decision,

(ii) if before the expiration of such period the court decides that such patent has been infringed, the approval may be made effective on such date as the court orders under section 271(e)(4)(A) of title 35, or

(iii) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not infringed, the approval shall be made effective on the date of such court decision.

In such an action, each of the parties shall reasonably cooperate in expediting the action. Until the expiration of forty-five days from the date the notice made under paragraph (3)(B) is received, no action may be brought under section 2201 of title 28 for a declaratory judgment with respect to the patent. Any action brought under such section 2201 shall be brought in the judicial district where the defendant has its principal place of business or a regular and established place of business.

(D)

(i) If an application (other than an abbreviated new drug application) submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of another application for a drug for

which the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted effective before the expiration of ten years from the date of the approval of the application previously approved under subsection (b) of this section.

(ii) If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application which refers to the drug for which the subsection (b) application was submitted and for which the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the

applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted may be submitted under subsection (b) of this section before the expiration of five years from the date of the approval of the application under subsection (b) of this section, except that such an application may be submitted under subsection (b) of this section after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in clause (iv) of subsection (b)(2)(A) of this section. The approval of such an application shall be made effective in accordance with this paragraph except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (C) shall be extended by such amount of time (if any) which is required

for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

(iii) If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) of this section for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the

applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

(iv) If a supplement to an application approved under subsection (b) of this section is approved after September 24, 1984, and the supplement contains reports of new clinical investigations (other than bioavailabilty [1] studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under subsection (b) of this section for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) of this section if the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not

conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted. "bioavailability".

(v) If an application (or supplement to an application) submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b) of this section, was approved during the period beginning January 1, 1982, and ending on September 24, 1984, the Secretary may not make the approval of an application submitted under this subsection and for which the investigations described in clause (A) of subsection (b)(1) of this section and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted

and which refers to the drug for which the subsection (b) application was submitted effective before the expiration of two years from September 24, 1984.

(4) A drug manufactured in a pilot or other small facility may be used to demonstrate the safety and effectiveness of the drug and to obtain approval for the drug prior to manufacture of the drug in a larger facility, unless the Secretary makes a determination that a full scale production facility is necessary to ensure the safety or effectiveness of the drug.

(d) Grounds for refusing application; approval of application; "substantial evidence" defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that

(1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof;

(2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions;

(3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity;

(4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or

(5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or

(6) the application failed to contain the patent information prescribed by subsection (b) of this section; or

(7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence

consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence.

(e) Withdrawal of approval; grounds; immediate suspension upon finding imminent hazard to public health

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds

(1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved;

(2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application

was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or

(3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or

(4) the patent information prescribed by subsection (c) of this section was not filed within thirty days after the receipt of written notice from the Secretary specifying the failure to file such information; or

(5) that the application contains any untrue statement of a material fact: Provided, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be

delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application submitted under subsection (b) or (j) of this section with respect to any drug under this section if the Secretary finds

(1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (k) of this section or to comply with the notice requirements of section 360(k)(2) of this title, or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsection; or

(2) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or

(3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false

or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based.

(f) Revocation of order refusing, withdrawing or suspending approval of application

Whenever the Secretary finds that the facts so require, he shall revoke any previous order under subsection (d) or (e) of this section refusing, withdrawing, or suspending approval of an application and shall approve such application or reinstate such approval, as may be appropriate.

(g) Service of orders

Orders of the Secretary issued under this section shall be served

(1) in person by any officer or employee of the department designated by the Secretary or

(2) by mailing the order by registered mail or by certified mail addressed to the applicant or respondent at his last-known address in the records of the Secretary.

(h) Appeal from order

An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals or the circuit wherein such applicant resides or has his principal place of

business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of title 28. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28. The commencement of proceedings under this subsection shall not, unless

specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

(i) Exemptions of drugs for research; discretionary and mandatory conditions; direct reports to Secretary

(1) The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of the public health, provide for conditioning such exemption upon -

(A) the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, of preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing;

(B) the manufacturer or the sponsor of the investigation of a new drug proposed to be distributed to investigators for clinical testing obtaining a signed agreement from each of such investigators that patients to whom the drug is administered will be under his

personal supervision, or under the supervision of investigators responsible to him, and that he will not supply such drug to any other investigator, or to clinics, for administration to human beings; and

(C) the establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application pursuant to subsection (b) of this section.

(2) Subject to paragraph (3), a clinical investigation of a new drug may begin 30 days after the Secretary has received from the manufacturer or sponsor of the investigation a submission containing such information about the drug and the clinical investigation, including -

(A) information on design of the investigation and adequate reports of basic information, certified by the applicant to be accurate reports, necessary to assess the safety of the drug for use in clinical investigation; and

(B) adequate information on the chemistry and manufacturing of the drug, controls available for the drug, and primary data tabulations from animal or human studies.

(3)

(A) At any time, the Secretary may prohibit the sponsor of an investigation from conducting the investigation (referred to in this paragraph as a "clinical hold") if the Secretary makes a determination described in subparagraph (B). The Secretary shall specify the basis for the clinical hold, including the specific information available to the Secretary which served as the basis for such clinical hold, and confirm such determination in writing.

(B) For purposes of subparagraph (A), a determination described in this subparagraph with respect to a clinical hold is that -

(i) the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation, taking into account the qualifications of the clinical investigators, information about the drug, the design of the clinical investigation, the condition for which the drug is to be investigated, and the health status of the subjects involved; or

(ii) the clinical hold should be issued for such other reasons as the Secretary may by regulation establish (including reasons established by regulation before November 21, 1997).

(C) Any written request to the Secretary from the sponsor of an investigation that a clinical hold be removed shall receive a decision, in writing and specifying the reasons therefor, within 30 days after receipt of such request. Any such request shall include sufficient information to support the removal of such clinical hold.

(4) Regulations under paragraph (1) shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational

purposes certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where it is not feasible or it is contrary to the best interests of such human beings. Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs.

21 CFR § 314.53
21 C.F.R. § 314.53

CODE OF FEDERAL REGULATIONS
TITLE 21 - FOOD AND DRUGS
CHAPTER I - FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER D - DRUGS FOR HUMAN USE
PART 314 - APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG
SUBPART B - APPLICATIONS

Current through November 12, 2002; 67 FR 68725

§ 314.53 Submission of patent information.

(a) Who must submit patent information. This section applies to any applicant who submits to FDA a new drug application or an amendment to it under section 505(b) of the act and § 314.50 or a supplement to an approved application under § 314.70, except as provided in paragraph (d)(2) of this section.

(b) Patents for which information must be submitted. An applicant described in paragraph (a) of this section shall submit information on each patent that claims the drug or a method of using the drug that is the subject of the new drug application or amendment or supplement to it and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. For purposes of this part, such patents consist of drug substance (ingredient) patents, drug product

(formulation and composition) patents, and method of use patents. Process patents are not covered by this section and information on process patents may not be submitted to FDA. For patents that claim a drug substance or drug product, the applicant shall submit information only on those patents that claim a drug product that is the subject of a pending or approved application, or that claim a drug substance that is a component of such a product. For patents that claim a method of use, the applicant shall submit information only on those patents that claim indications or other conditions of use of a pending or approved application.

(c) Reporting requirements -

(1) General requirements. An applicant described in paragraph (a) of this section shall submit the following information for each patent described in paragraph (b) of this section:

(i) Patent number and the date on which the patent will expire.

(ii) Type of patent, i.e., drug, drug product, or method of use.

(iii) Name of the patent owner.

(iv) If the patent owner or applicant does not reside or have a place of business within the United States, the name of an agent (representative) of the patent owner or applicant who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the act and §§ 314.52 and 314.95.

(2) Formulation, composition, or method of use patents-

(i) Original declaration. For each formulation, composition, or method of use patent, in addition to the patent information described in paragraph (C)(1) of this section the applicant shall submit the following declaration:

The undersigned declares that Patent No. ___ covers the formulation, composition, and/or method of use of (name of drug product). This product is (currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act) [or] (the subject of this application for which approval is being sought):

_____

_____

(ii) Amendment of patent information upon approval. Within 30 days after the date of approval of its application, if the application contained a declaration required under paragraph (c)(2)(i) of this section, the applicant shall by letter amend the declaration to identify each patent that claims the formulation, composition, or the specific indications or other conditions of use that have been approved.

(3) No relevant patents. If the applicant believes that there are no patents which claim the drug or the drug product or which claim a method of using the drug product and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product, it shall so declare.

(4) Authorized signature. The declarations required by this section shall be signed by the applicant or patent owner, or the applicant's or patent owner's attorney, agent (representative), or other authorized official.

(d) When and where to submit patent information –

(1) Original application. An applicant shall submit with its original application submitted under this part, including an application described in section 505(b)(2) of the act, the information described in paragraph (c) of this section on each drug (ingredient), drug product (formulation and composition), and method of use patent issued before the application is filed with FDA and for which patent information is required to be submitted under this section. If a patent is issued after the application is filed with FDA but before the application is approved, the applicant shall, within 30 days of the date of issuance of the patent, submit the required patent information in an amendment to the application under § 314.60.

(2) Supplements.

(i) An applicant shall submit patent information required under paragraph (c) of this section for a patent that claims the drug, drug product, or method of use for which approval is sought in any of the following supplements:

(A) To change the formulation;

(B) To add a new indication or other condition of use, including a change in route of administration;

(C) To change the strength;

(D) To make any other patented change regarding the drug, drug product, or any method of use.

(ii) If the applicant submits a supplement for one of the changes listed under paragraph (d)(2)(i) of this section and existing patents for which information has already been submitted to FDA claim the changed product, the applicant shall submit a certification with the supplement identifying the patents that claim the changed product.

(iii) If the applicant submits a supplement for one of the changes listed under paragraph (d)(2)(i) of this section and no patents, including previously submitted patents, claim the changed product, it shall so certify.

(iv) The applicant shall comply with the requirements for amendment of formulation or composition and method of use patent information under paragraphs (c)(2)(ii) and (d)(3) of this section.

(3) Patent information deadline. If a patent is issued for a drug, drug product, or method of use after an application is approved, the applicant shall submit to FDA the required patent information within 30 days of the date of issuance of the patent.

(4) Copies. The applicant shall submit two copies of each submission of patent information, an archival copy and a copy for the chemistry, manufacturing, and controls section of the review copy, to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, Park Bldg., rm. 2-14, 12420 Parklawn Dr., Rockville, MD 20857. The applicant shall submit the patent information by letter separate from, but at the same time as, submission of the supplement.

(5) Submission date. Patent information shall be considered to be submitted to FDA as of the date the information is received by the Central Document Room.

(6) Identification. Each submission of patent information, except information submitted with an original application, and its mailing cover shall bear prominent identification as to its contents, i.e., "Patent Information," or, if submitted after approval of an application. "Time Sensitive Patent Information."

(e) Public disclosure of patent information. FDA will publish in the list the patent number and expiration date of each patent that is required to be, and is, submitted to FDA by an applicant, and for each use patent, the approved indications or other conditions of use covered by a patent. FDA will publish such patent information upon approval of the application, or, if the patent information is submitted by the applicant after approval of an application as provided under paragraph (d)(2) of this section, as soon as possible after the submission to the agency of the patent information. Patent information submitted by the last working day of a month will be published in that month's supplement to the list. Patent information received by the agency between monthly publication of supplements to the list will be placed on public display in FDA's Freedom of Information Staff. A request for copies of the file shall be sent in writing to the Freedom of Information Staff (HFI-35), Food and Drug Administration, rm. 12A-16, 5600 Fishers Lane, Rockville, MD 20857.

(f) Correction of patent information errors. If any person disputes the accuracy or relevance of patent information submitted to the agency under this section and published by FDA in the list, or believes that an applicant has failed to submit required patent information, that person must first notify the agency in writing stating the grounds for disagreement. Such notification should be directed to the Drug Information Services Branch (HFD-84), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. The agency will then request of the applicable new drug application holder that the correctness of the patent information or omission of patent information be confirmed. Unless the application holder withdraws or amends its patent information in response to FDA's request, the agency will not change the patent information in the list. If the new drug application holder does not change the patent

information submitted to FDA, a 505(b)(2) application or an abbreviated new drug application under section 505(j) of the act submitted for a drug that is claimed by a patent for which information has been submitted must, despite any disagreement as to the correctness of the patent information, contain an appropriate certification for each listed patent.

[59 FR 50363, Oct. 3, 1994]

<General Materials (GM) - References, Annotations, or Tables>

21 C.F.R. § 314.53

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END OF DOCUMENT